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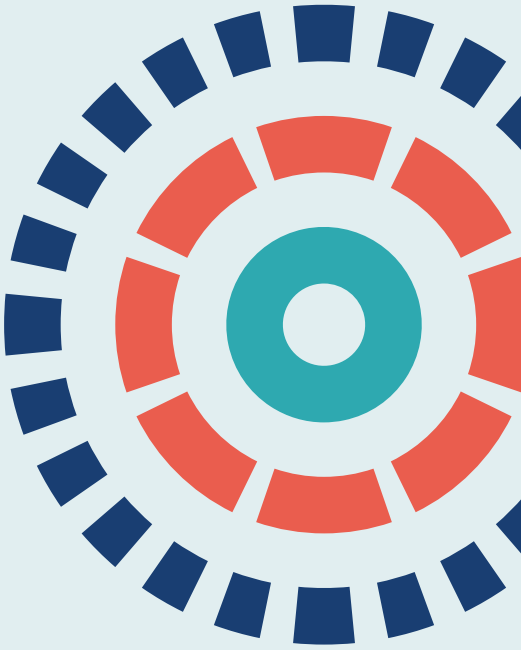

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Abstract

Sodium bicarbonate to improve physical function in patients over 60 years with advanced chronic kidney disease: the BiCARB RCT

Miles D Witham,[1,2]* Margaret Band,[3] Huey Chong,[4] Peter T Donnan,[5] Geeta Hampson,[6] May Khei Hu,[7] Roberta Littleford,[8] Edmund Lamb,[9] Philip A Kalra,[10] Gwen Kennedy,[11] Paul McNamee,[4] Deirdre Plews,[3] Petra Rauchhaus,[3] Roy L Soiza,[12] Deepa Sumukadas,[13] Graham Warwick[14] and Alison Avenell[15]

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Background: Advanced chronic kidney disease is common in older people and is frequently accompanied by metabolic acidosis. Oral sodium bicarbonate is used to treat this acidosis, but evidence is lacking on whether or not this provides a net gain in health or quality of life for older people.

Objectives: The objectives were to determine whether or not oral bicarbonate therapy improves physical function, quality of life, markers of renal function, bone turnover and vascular health compared with placebo in older people with chronic kidney disease and mild acidosis; to assess the safety of oral bicarbonate; and to establish whether or not oral bicarbonate therapy is cost-effective in this setting.

Design: A parallel-group, double-blind, placebo-controlled randomised trial.

Setting: The setting was nephrology and geriatric medicine outpatient departments in 27 UK hospitals.

Participants: Participants were adults aged ≥ 60 years with advanced chronic kidney disease (glomerular filtration rate category 4 or 5, not on dialysis) with a serum bicarbonate concentration of < 22 mmol/l.

Interventions: Eligible participants were randomised 1 : 1 to oral sodium bicarbonate or matching placebo. Dosing started at 500 mg three times daily, increasing to 1 g three times daily if the serum bicarbonate concentration was < 22 mmol/l at 3 months.

Main outcome measures: The primary outcome was the between-group difference in the Short Physical Performance Battery score at 12 months, adjusted for baseline. Other outcome measures included generic and disease-specific health-related quality of life, anthropometry, 6-minute walk speed, grip strength, renal function, markers of bone turnover, blood pressure and brain natriuretic peptide. All adverse events were recorded, including commencement of renal replacement therapy. For the health economic analysis, the incremental cost per quality-adjusted life-year was the main outcome.

Results: In total, 300 participants were randomised, 152 to bicarbonate and 148 to placebo. The mean age of participants was 74 years and 86 (29%) were female. Adherence to study medication was 73% in both groups. A total of 220 (73%) participants were assessed at the 12-month visit. No significant treatment effect was evident for the primary outcome of the between-group difference in the Short Physical Performance Battery score at 12 months (–0.4 points, 95% confidence interval –0.9 to 0.1 points; $p = 0.15$). No significant treatment benefit was seen for any of the secondary outcomes. Adverse events were more frequent in the bicarbonate arm (457 vs. 400). Time to commencement of renal replacement therapy was similar in both groups (hazard ratio 1.22, 95% confidence interval 0.74 to 2.02; $p = 0.43$). Health economic analysis showed higher costs and lower quality of life in the bicarbonate arm at 1 year, with additional costs of £564 (95% confidence interval £88 to £1154) and a quality-adjusted life-year difference of –0.05 (95% confidence interval –0.08 to –0.01); placebo dominated bicarbonate under all sensitivity analyses for incremental cost-effectiveness.

Limitations: The trial population was predominantly white and male, limiting generalisability. The increment in serum bicarbonate concentrations achieved was small and a benefit from larger doses of bicarbonate cannot be excluded.

Conclusions: Oral sodium bicarbonate did not improve a range of health measures in people aged ≥ 60 years with chronic kidney disease category 4 or 5 and mild acidosis, and is unlikely to be cost-effective for use in the NHS in this patient group. Once other current trials of bicarbonate therapy in chronic kidney disease are complete, an individual participant meta-analysis would be helpful to determine which subgroups, if any, are more likely to benefit and which treatment regimens are more beneficial.

Trial registration: Current Controlled Trials ISRCTN09486651 and EudraCT 2011-005271-16. The systematic review is registered as PROSPERO CRD42018112908.

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Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/hta24270).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

CI	confidence interval
CKD	chronic kidney disease
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
eGFR	estimated glomerular filtration rate
EQ-5D	EuroQoL-5 Dimensions
EQ-5D-3L	EuroQoL-5 Dimensions, three-level version
GFR	glomerular filtration rate
GP	general practitioner
HbA_{1c}	glycosylated haemoglobin
HR	hazard ratio
HTA	Health Technology Assessment
ICECAP	Investigating Choice Experiments for the preferences of older people CAPability
ICECAP-O	Investigating Choice Experiments for the preferences of older people CAPability-older people
KDQoL	Kidney Disease Quality of Life
MCID	minimum clinically important difference
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PTH	parathyroid hormone
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SF-36	Short Form questionnaire-36 items
SPPB	Short Physical Performance Battery
TMG	Trial Management Group
TRuST	Tayside Randomisation SysTem
TSC	Trial Steering Committee

Plain English summary

Patients with advanced chronic kidney disease often have excessive levels of acid in their blood (acidosis). Acidosis has been associated with a range of other problems that particularly affect patients with chronic kidney disease, including weaker muscles, weaker bones, worse blood vessel health and kidney disease that worsens more quickly. For decades, acidosis has been treated with sodium bicarbonate tablets (the ingredient found in baking soda) to neutralise the excess acid. However, sodium bicarbonate is awkward to take, may cause side effects and may increase blood pressure.

To clarify whether or not sodium bicarbonate caused an overall improvement in health, we carried out a study involving 300 people aged ≥ 60 years with advanced chronic kidney disease and mild acidosis. Half received sodium bicarbonate capsules and half received dummy capsules (placebo), for up to 2 years. The treatments were chosen randomly by a computer and the participants, their doctors and the researchers were not aware of the treatment received until the end of the study. We measured physical function (walking speed, ability to stand from a chair, balance) alongside quality of life, kidney function, bone and blood vessel health, side effects and health service use over 2 years.

We found that sodium bicarbonate did not improve physical function or quality of life compared with placebo. Sodium bicarbonate also did not improve kidney function, bone health or blood vessel health compared with placebo. More people in the sodium bicarbonate group than in the placebo group had side effects, although blood pressure was the same in both groups. Health-care costs were higher in the sodium bicarbonate group than in the placebo group. We conclude that oral sodium bicarbonate did not significantly improve health measures compared with placebo for older people (aged ≥ 60 years) with advanced chronic kidney disease associated with mild acidosis.

Scientific summary

Background

Chronic kidney disease becomes increasingly common with advancing age, with approximately 2% of the population aged ≥ 70 years suffering from advanced (glomerular filtration rate category 4 or 5) chronic kidney disease. Advanced chronic kidney disease is often accompanied by metabolic acidosis because of the inability of the kidneys to excrete sufficient excess acid. Acidosis has been associated with a range of adverse health outcomes in patients with chronic kidney disease, including worse cardiovascular health, weaker bones, weaker muscles and more rapid progression of kidney disease. As a result, oral sodium bicarbonate has been used for decades to counteract metabolic acidosis. Few trials have tested whether or not sodium bicarbonate is effective at countering these adverse outcomes. Sodium bicarbonate also carries risks of gastrointestinal side effects and is awkward for patients to take, and there are concerns that the sodium content might increase blood pressure or fluid overload. These issues are of particular relevance for older people, who make up the majority of people in the UK with advanced kidney disease and who are most likely to suffer side effects because of coexisting multimorbidity and polypharmacy.

Objectives

The primary objective of the BiCARB trial was to determine whether or not oral bicarbonate therapy improves physical function compared with placebo in older people with chronic kidney disease and mild acidosis.

The secondary objectives were to:

- determine whether or not oral bicarbonate therapy improves health-related quality of life compared with placebo
- compare the impact of oral bicarbonate therapy with that of placebo on biochemical markers of chronic kidney disease
- assess whether or not use of oral bicarbonate therapy is associated with an excess of adverse events compared with placebo
- estimate the cost-effectiveness of using oral bicarbonate therapy compared with placebo
- assess the effect of oral bicarbonate therapy compared with placebo on bone turnover and vascular health, as assessed by biochemical markers.

Methods

The study was a parallel-group, double-blind, placebo-controlled randomised trial. Participants were recruited from nephrology and geriatric medicine outpatient departments in UK hospitals. Participants were eligible for inclusion if they were aged ≥ 60 years with advanced chronic kidney disease (glomerular filtration rate category 4 or 5, not on dialysis) with a serum bicarbonate concentration of < 22 mmol/l. Participants were excluded if they were currently taking bicarbonate, had a diagnosis of renal tubular acidosis, were taking bisphosphonate drugs, were on or would soon start renal replacement therapy, were terminally ill, could not give written informed consent, had uncontrolled hypertension or decompensated chronic heart failure, were participating in another clinical trial or were allergic to sodium bicarbonate tablets or lactose (used as an excipient in the tablets). Eligible participants were randomised 1 : 1 to oral sodium bicarbonate tablets or identical matching placebo tablets using a web-based randomisation system to conceal allocation. Dosing started at 500 mg three times per day and was increased to 1 g three times per day if the serum bicarbonate concentration was < 22 mmol/l at the 3-month visit.

Outcomes were collected at baseline and 3, 6, 12 and 24 months. The primary outcome was the between-group difference in the Short Physical Performance Battery score (a measure of lower limb strength and balance that predicts future disability, need for care and death) at 12 months, adjusted for baseline values. The initial sample size calculation estimated that 380 participants were required to detect a 1-point difference between groups in the Short Physical Performance Battery score at 12 months with 90% power, assuming a standard deviation of 2.6, an alpha of 0.05 and a dropout rate of 10% every 6 months. Sample size re-estimation prior to closing recruitment indicated that 300 participants would have 87% power to detect the 1-point difference in the Short Physical Performance Battery score after adjusting for baseline values. Secondary outcome measures included generic (EuroQoL-5 Dimensions, three-level version) and disease-specific (Kidney Disease Quality of Life) health-related quality of life questionnaires; anthropometry (weight, mid-arm muscle circumference, triceps skinfold thickness, mid-thigh circumference); physical performance (6-minute walk speed, grip strength); renal function measured using creatinine, cystatin C and the urinary albumin-to-creatinine ratio; markers of bone turnover and mineral metabolism (serum calcium, serum phosphate, bone-specific alkaline phosphatase, tartrate-resistant acid phosphatase 5b, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D); vascular health (blood pressure, B-type natriuretic peptide and serum cholesterol); and other relevant biochemical markers, including haemoglobin, thyroid-stimulating hormone and serum albumin. All adverse events were recorded, including commencement of renal replacement therapy. Falls were recorded prospectively using a self-completed falls diary. For the health economic analysis, information on health and social care use was collected at each follow-up visit and was combined with quality of life measures to derive the incremental cost per quality-adjusted life-year.

Analyses were prespecified in statistical analysis plans and conducted in accordance with intention-to-treat principles. The primary outcome (between-group difference in the Short Physical Performance Battery at 12 months) was analysed using linear mixed models, adjusted for baseline measurements, minimisation variables (age, sex and stage of chronic kidney disease) and a random effect variable for recruitment site. Preplanned subgroup analyses were conducted for age, sex, baseline chronic kidney disease stage, baseline bicarbonate level, baseline Short Physical Performance Battery score and high versus low adherence. Secondary outcomes were analysed using repeated-measures models, adjusted for baseline values and minimisation variables as above. Time-to-event analyses (time to death, time to commencement of renal replacement therapy) were conducted using Cox proportional hazards models, adjusted for minimisation variables as above. For all analyses, a two-sided p-value of < 0.05 was taken as significant, with no adjustment for multiple testing. For the health economic analysis, a cost–utility analysis was undertaken that involved estimation of the incremental costs and incremental effects, measured using quality-adjusted life-years, based on responses to the EuroQoL-5 Dimensions, three-level version, instrument. Estimation was performed using generalised linear regression modelling, with adjustment for skewed data and for baseline differences in cost, EuroQoL-5 Dimensions, three-level version, score and other patient characteristics (age, sex, chronic kidney disease stage). Non-parametric bootstrap methods were used for calculating confidence intervals around cost and quality-adjusted life-year differences. Cost-effectiveness acceptability curves were employed to show the probability that bicarbonate therapy was cost-effective for different values of willingness to pay per additional quality-adjusted life-year.

Results

We randomised 300 participants from 27 UK nephrology and geriatric medicine outpatient centres between May 2013 and February 2017. In total, 152 were allocated to bicarbonate and 148 were allocated to placebo. The mean age of participants was 74 years and 86 (29%) were female. The Short Physical Performance Battery score at baseline was 8.0 and 8.1 points in the bicarbonate and placebo arms, respectively, denoting substantially impaired physical performance. Adherence to study medication was 73% in both groups. A total of 116 (76%) and 104 (70%) participants were assessed at the 12-month visit in the bicarbonate and placebo groups, respectively. The mean dose of bicarbonate prescribed was 1.88 g per day, with a mean dose of 1.39 g per day ingested. The serum bicarbonate concentration was, on average, 1.1 mmol/l higher in the bicarbonate group than in the placebo group over the whole course of the trial.

No significant treatment effect was evident for the primary outcome of the between-group difference in the Short Physical Performance Battery score at 12 months (–0.4 points, 95% confidence interval –0.9 to 0.1 points; $p = 0.15$). Very similar results were found in sensitivity analyses using multiple imputation of missing data. Subgroup analyses showed no significant difference in treatment effect based on age (< 75 vs. ≥ 75 years), sex, baseline chronic kidney disease category (4 vs. 5), baseline bicarbonate level (< 18 vs. ≥ 18 mmol/l) or baseline Short Physical Performance Battery score (< 10 vs. ≥ 10 points). Participants with adherence above and below the prespecified 80% threshold showed similar treatment effects according to the Short Physical Performance Battery score at 12 months (adherence > 80%: –0.6 points, 95% confidence interval –1.3 to 0.1 points; adherence ≤ 80%: 0.0 points, 95% confidence interval –0.7 to 0.7 points). These results excluded the minimum clinically important improvement for the Short Physical Performance Battery (of 1 point) with a high degree of confidence.

No significant treatment benefit was seen for any of the secondary outcomes, including quality of life, anthropometry, N-terminal pro-B-type natriuretic peptide and markers of bone turnover and mineral metabolism. Of particular note is that there was no significant treatment effect on estimated glomerular filtration rate (repeated-measures treatment effect 0.6 ml/minute/1.73 m^2, 95% confidence interval –0.8 to 2.0 ml/minute/1.73 m^2; $p = 0.39$). Measures of physical performance were worse in the bicarbonate arm than in the placebo arm when considered across all visits: Short Physical Performance Battery treatment effect –0.6 points (95% confidence interval –1.0 to –0.1 points; $p = 0.02$); 6-minute walk treatment effect –33 m (95% confidence interval –62 to –4 m; $p = 0.02$); and handgrip strength –1.5 kg (95% confidence interval –2.8 to –0.2 kg; $p = 0.03$). Blood pressure was no higher in the bicarbonate arm than in the placebo arm: repeated-measures treatment effect for systolic blood pressure 0 mmHg (95% confidence interval –4 to 3 mmHg; $p = 0.93$) and repeated-measures treatment effect for diastolic blood pressure –1 mmHg (95% confidence interval –3 to 1 mmHg; $p = 0.16$).

Adverse events were more frequent in the bicarbonate arm than in the placebo arm (457 vs. 400, respectively), driven in part by higher rates of gastrointestinal adverse events, but also by higher rates of cardiovascular and respiratory adverse events. Thirty-three participants commenced renal replacement therapy (dialysis or transplantation) in each group during the trial. Time to commencement of renal replacement therapy was similar in both groups (hazard ratio 1.22, 95% confidence interval 0.74 to 2.02; $p = 0.43$). There were 15 deaths in the bicarbonate group compared with 11 in the placebo group. The time to death was not significantly different between the two groups (hazard ratio 1.30, 95% confidence interval 0.60 to 2.83; $p = 0.51$). There were more falls among participants in the bicarbonate group than among participants in the placebo group (49 vs. 39, respectively); the fall rate per participant was not significantly different in the two arms: bicarbonate, 0.99 falls per year (95% confidence interval 0.61 to 1.38 falls per year); placebo, 0.72 falls per year (95% confidence interval 0.25 to 1.19 falls per year).

Health economic analysis showed higher costs and lower quality of life in the bicarbonate arm at 1 year, with additional costs of £564 (95% confidence interval £88 to £1154) and a quality-adjusted life-year difference of –0.05 (95% confidence interval –0.08 to –0.01). Similar differences were also found at 2 years' follow-up. In further analyses, the addition of the costs of renal replacement for renal replacement patients who were lost to follow-up led to a non-significant additional cost of £809 (95% confidence interval –£4125 to £5412) in the bicarbonate arm over 24 months. A series of one-way sensitivity analyses was conducted [lower generic prescribing costs, lower cost per day, lower and higher dialysis costs, use of ICECAP (Investigating Choice Experiments for the preferences of older people CAPability) values rather than EuroQoL-5 Dimensions, three-level version, values and quality-adjusted life-years]. In all sensitivity analyses, patients in the placebo group were estimated to have lower costs and a better quality of life. Excluding dialysis patients who were lost to follow-up and their renal replacement costs, the probability of sodium bicarbonate being more cost-effective than placebo was close to zero in all analyses. The inclusion of dialysis costs for patients who dropped out of the trial after commencement of dialysis led to non-significant additional costs in the bicarbonate arm, and the probability of sodium bicarbonate being more cost-effective than placebo was found to be between 15% and 20%. Placebo dominated bicarbonate under all sensitivity analyses for incremental cost-effectiveness.

Conclusions: implications for health care

The results from this pragmatic, multicentre, placebo-controlled trial suggest that, at least for older patients in chronic kidney disease category 4 or 5, 1.5–3 g per day of oral bicarbonate did not produce any health benefits and may be associated with net harms. Although other indications for the control of acidosis exist (e.g. high potassium concentrations), evidence from the current trial suggests that the additional cost, treatment burden and side effects of oral bicarbonate may not justify its routine use in older people with advanced chronic kidney disease and mild acidosis.

Suggestions for further research

Other trials of bicarbonate are in progress. Once complete, an individual participant meta-analysis should be conducted, examining the effects of bicarbonate therapy on physical function, quality of life, renal function and progression to renal replacement therapy, anthropometry, and bone and vascular health. Such a meta-analysis should also seek to pool adverse events, particularly cardiovascular events, and to identify the characteristics of those most likely to respond to bicarbonate therapy, if any.

Depending on the results of meta-analyses, it may be necessary to formally test the effectiveness of bicarbonate therapy in other groups with chronic kidney disease, for example younger patients or those with lower serum bicarbonate concentrations, in randomised controlled trials. Alternative methods to manage acidosis in advanced chronic kidney disease need to be tested, either different bicarbonate treatment strategies, such as dose titration to target, or novel methods of managing acidosis that do not rely on the use of bicarbonate.

A final, broader recommendation is that there is a need to design and execute more trials like the BiCARB trial, focusing on outcomes that are important to older patients both in the field of chronic kidney disease and, more widely, in other organ-specific fields of clinical practice.

Trial registration

This trial is registered as ISRCTN09486651 and EudraCT 2011-005271-16. The systematic review is registered as PROSPERO CRD42018112908.

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Chapter 1 Introduction

In 2010, the Health Technology Assessment (HTA) programme of the National Institute for Health Research (NIHR) commissioned a randomised controlled trial (RCT) to address the clinical effectiveness and cost-effectiveness of oral sodium bicarbonate therapy for older people with advanced chronic kidney disease (CKD) and mild metabolic acidosis. This monograph reports the findings of the multicentre RCT conducted to address that brief.

The BiCARB trial was a large, multicentre RCT, the aim of which was to determine whether or not oral sodium bicarbonate therapy is more effective than placebo at improving physical function and quality of life in patients aged ≥ 60 years with CKD [glomerular filtration rate (GFR) category 4 or 5 (< 30 ml/minute/1.73 m^2), not on renal replacement therapy] and mild metabolic acidosis.

Background and rationale for the trial

Chronic kidney disease is common; 6.1% of the English population have an estimated GFR (eGFR) of < 60 ml/minute/1.73 m^2 (i.e. GFR category 3–5 in the international CKD staging system),[1] and rates in people aged > 70 years are five times higher than this.[2] Population-based estimates suggest a prevalence of severe CKD (eGFR 15–29 ml/minute/1.73 m^2, equivalent to GFR category 4) of approximately 2% in those aged ≥ 70 years,[3] and approximately 20% of such patients will have a degree of metabolic acidosis (often operationalised as a serum bicarbonate level of < 22 mmol/l), with rates increasing as renal function declines.[4] As discussed in the following sections, metabolic acidosis has been associated with multiple adverse outcomes, including impaired bone health and vascular health, accelerated renal decline and impaired physical function. The extent to which acidosis is causal for these phenomena, as opposed to associations being the result of residual confounding by other unmeasured factors present in patients with CKD, remains unclear.

Association with progression of renal dysfunction

Several studies have linked the presence of lower serum bicarbonate concentrations to accelerated decline in renal function.[5,6] There is debate as to how many of these observed associations are due to low bicarbonate concentration independent of renal function. Recent pooled data from two large RCTs suggested that lower baseline bicarbonate concentrations correlate with faster decline in GFR and a higher probability of reaching kidney failure, but this association disappeared after adjusting for baseline GFR.[7] In the Modification of Diet in Renal Disease (MDRD) study cohort, serum bicarbonate was not associated with progression to end-stage renal failure or death after adjustment for baseline GFR.[5] Conversely, other studies have found that the association between low serum bicarbonate and accelerated decline in renal function remains even after adjustment for baseline GFR.[8]

Association with cardiovascular disease

In the cardiovascular system, acidosis has been associated with increased levels of endothelin and aldosterone, chronic inflammation and endothelial dysfunction.[9–11] There is a lack of evidence of an association between low serum bicarbonate and increased vascular events.[7,12] An elevated serum bicarbonate concentration may, however, be associated with deleterious outcomes, and concern persists that administration of the sodium load that accompanies bicarbonate administration could increase blood pressure.[13]

Association with physical function

Recent data suggest an association between lower serum bicarbonate concentrations and impaired physical function, even in patients without advanced CKD.[14] Importantly, for older patients with CKD, low serum bicarbonate also predicts future onset of functional limitations (defined as difficulty walking one-quarter of a mile or climbing 10 steps). Those with a serum bicarbonate concentration of < 23 mmol/l were 1.6 times more likely to develop a functional limitation than those with a baseline serum bicarbonate concentration of

≥ 26 mmol/l, even after adjustment for the presence of CKD.[15] Sarcopenia (the loss of muscle mass and strength) is common in advanced CKD and may, in part, be driven by acidosis, which stimulates muscle proteolysis.[16]

Association with bone health

An acidic environment can have direct effects on the skeleton by increasing bone resorption while reducing osteoblastic bone formation. Other contributory pathological consequences include its indirect effects on parathyroid hormone (PTH) and/or vitamin D metabolism. Acidosis has been shown to affect PTH release, as well as the cellular response to PTH, and inhibits PTH-induced 1,25-dihydroxyvitamin D formation by suppressing 1-alpha-hydroxylase activity.[17] Acidosis produces an inflammatory state with the production of cytokines such as interleukin 6 and tumour necrosis factor alpha, which promote osteoclastic bone resorption. These abnormalities can not only exacerbate the bone and mineral abnormalities associated with CKD but can also lead to osteoporosis. Bone mineral density is adversely affected by acidosis in CKD, although the effect on fracture rate remains unclear; few data exist on fracture rates in patients with CKD not undergoing dialysis.[18–20]

Review of existing trial evidence

As part of the preparation for this report, we undertook a systematic review to synthesise current trial evidence in this area. The search strategy for this systematic review is provided in *Appendix 1*; details of included studies are provided in *Table 23* (see *Appendix 2*) and forest plots for the main meta-analysed outcomes are provided in *Figures 19–25* (see *Appendix 2*). The systematic review was registered on the PROSPERO database (CRD42018112908). Evidence available prior to completion of the BiCARB trial is discussed here and has been published along with the full methods;[21] meta-analyses were then repeated with the addition of results from the BiCARB trial and these results are discussed in *Chapter 6*.

Key findings from the systematic review

In total, seven trials were eligible for inclusion,[22–28] recruiting a total of 815 participants with CKD not on dialysis. Trial size ranged from 40 to 188 participants, the mean age of participants ranged from 40 to 65 years and follow-up ranged from 3 months to 5 years. Most trials included participants with a baseline bicarbonate concentration within the normal range (i.e. 22 to 30 mmol/l) and compared strategies of bicarbonate replacement (titration to target levels) rather than administering fixed bicarbonate doses. The quality of the trials was poor to moderate, with all seven trials failing to adequately mask participants and clinicians, and the effectiveness of masking of research teams being unclear in five of the seven trials.

The overall treatment effect on bicarbonate concentrations seen in the trials was a mean increase from supplementation of 3.4 mmol/l [95% confidence interval (CI) 1.9 to 4.9 mmol/l]. Marked heterogeneity in the time points used for follow-up makes comparison across trials challenging, but the treatment effect on bicarbonate concentrations at 1 year was a mean increase of 3.2 mmol/l (95% CI 2.0 to 4.3 mmol/l). The eGFR was modestly higher in the intervention groups than in the control groups at the last follow-up time point (mean difference 3.1 ml/minute/1.73 m^2, 95% CI 1.3 to 4.9 ml/minute/1.73 m^2) but was not significantly different when confining analyses to 1-year outcomes only (mean difference 1.4 ml/minute/1.73 m^2, 95% CI –0.7 to 3.4 ml/minute/1.73 m^2). Too few trials reported the rate of change of eGFR to meta-analyse this outcome.

Systolic blood pressure was modestly but significantly higher in the intervention groups than in the control groups overall (mean difference 2.1 mmHg, 95% CI –1.0 to 5.2 mmHg); 1-year comparisons could not be made. Body weight and mid-arm muscle circumference (a measure of lean body mass) showed small, non-significant improvements in the meta-analysis from supplementation. No studies reported measures of physical performance or quality of life. Insufficient events were recorded to enable a judgement to be made about whether or not bicarbonate treatment reduced the risk of commencing dialysis or

transplantation. One study recorded four participants commencing dialysis in the bicarbonate arm and 22 in the control arm;[23] another study recorded three participants commencing dialysis in the bicarbonate arm and four in the control arm.[28]

In summary, existing data from before the BiCARB trial do not shed light on whether or not bicarbonate therapy improves physical function or quality of life for older patients with CKD and acidosis; there is significant uncertainty about as to whether bicarbonate therapy can improve or mitigate the decline in renal function seen in advanced CKD, and there is uncertainty as to whether bicarbonate therapy worsens blood pressure control and thus could increase the risk of cardiovascular events.

Potential deleterious effects of bicarbonate

Oral bicarbonate is inexpensive and has been used for many years. For some clinicians, the default position is to presume that the potential benefits are likely to exceed the risks of what is perceived to be a very safe intervention. Oral bicarbonate is not easy for patients to take – the tablets are large and multiple tablets usually need to be taken each day. Older patients are more likely to have dysphagia or a dry mouth and are already subject to polypharmacy. Sodium bicarbonate contains 6 mmol of sodium per 500 mg and a typical daily dose in current nephrology practice is up to 3 g per day, equivalent to the amount of sodium in 0.8 g of table salt. Concerns persist that this sodium load may lead to increased blood pressure and fluid overload. An additional concern is that, by raising the blood pH, calcium phosphate may be more likely to precipitate out into blood vessel walls, worsening vascular calcification.[29] Finally, gastrointestinal side effects (such as abdominal discomfort and bloating) are listed in the Summary of Product Characteristics (see *Report Supplementary Material 4*); these probably occur as a result of the generation of carbon dioxide in the gut through interaction with stomach acid.

Current guidelines

The introduction of routine eGFR reporting by laboratories has increased the number of older patients diagnosed with CKD[30] and bicarbonate is often used to treat older people with a low serum bicarbonate concentration. Trial evidence to underpin the effectiveness and safety of this intervention is, however, lacking and this lack of evidence is reflected in current guidelines, including Kidney Disease: Improving Global Outcomes (KDIGO)[31] and UK National Institute for Health and Care Excellence (NICE) guidelines,[32] which either give guidance based on expert consensus without underpinning evidence or note that it is not currently possible to make an evidence-based recommendation regarding the correction of mild to moderate metabolic acidosis in CKD. Clinical practice varies in the use of bicarbonate therapy for patients with CKD. Measurement and correction of acidosis is often part of standard care for patients managed under renal services but is less common for patients managed by primary care or geriatric medicine services.

Imperative for the current trial

Few trials to date have included many older people with CKD, despite older people being the group most likely to have CKD. CKD in older patients is almost always accompanied by multimorbidity and thus a narrow focus on measures of kidney disease alone is unlikely to reflect what is important to the patient. Any trial seeking to provide a comprehensive view of the net health gain or loss from treatment in older patients with CKD must therefore measure a range of outcomes of relevance to older people and must seek evidence of both benefit and harm, an approach that is more likely to provide appropriate evidence on which to base guidelines.

Chronic kidney disease is common and affects many older people. The accompanying acidosis may worsen the muscle weakness that affects many older people, as discussed above, with muscle weakness being a key risk factor for falls, disability, institutionalisation and premature death.[33] Only a minority of older people with CKD progress to a point where they require dialysis for renal failure. However, the effect on quality of life, and the cost burden from dialysis, are considerable; the cost burden is between £20,000

and £25,000 per patient per year, depending on modality and dialysis setting.[34] Finally, cardiovascular disease is the leading cause of hospitalisation and death in older people and is responsible itself for half to one-third of the decline in physical function seen with age.

An intervention that successfully reverses acidosis in this older population may therefore be able to simultaneously improve multiple important associated comorbidities in older people, with consequent improvements in function and quality of life, as well as potential reductions in hospitalisation and later institutionalisation.

Trial objectives

The primary objective of the BiCARB trial was to determine whether or not oral bicarbonate therapy improves physical function compared with placebo in older people with CKD and mild acidosis. The secondary objectives were to (1) determine whether or not oral bicarbonate therapy improves health-related quality of life compared with placebo; (2) compare the impact of oral bicarbonate therapy with that of placebo on biochemical markers of CKD; (3) assess whether or not use of oral bicarbonate therapy is associated with an excess of adverse events compared with placebo; (4) estimate the cost-effectiveness of using oral bicarbonate therapy compared with placebo; and (5) assess the effect of oral bicarbonate therapy compared with placebo on bone turnover and vascular health, as assessed by biochemical markers.

The protocol has been previously published by the authors in Witham *et al.*[35] This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly credited.

Chapter 2 Trial design

The trial was a randomised, double-blind, parallel-group, placebo-controlled trial, analysed according to intention-to-treat principles. The treatment and follow-up were planned to last for up to 2 years for each participant.

Participants

Target population for the trial

The original commissioning brief for the trial stipulated a target population of older patients with advanced CKD (stage 4 or 5, not on dialysis) and mild acidosis (serum bicarbonate concentration of < 22 mmol/l); our inclusion and exclusion criteria reflected these points.

Inclusion and exclusion criteria

Participants were recruited from primary and secondary care, including nephrology, geriatric medicine and general medicine clinics, according to the following inclusion and exclusion criteria:

- inclusion criteria –
  - willing and able to give informed consent for participation in the study
  - male or female aged ≥ 60 years
  - last known eGFR < 30 ml/minute/1.73 m^2 according to the MDRD4 equation[36]
  - serum bicarbonate concentration < 22 mmol/l
  - able (in the investigator's opinion) and willing to comply with all study requirements.
- exclusion criteria –
  - severe cognitive impairment precluding written informed consent
  - already taking bicarbonate therapy unless a 3-month washout period is planned
  - documented renal tubular acidosis
  - on renal replacement therapy (haemodialysis or peritoneal dialysis)
  - anticipated to start renal replacement therapy within 3 months
  - terminally ill, defined as < 3 months' expected survival
  - decompensated chronic heart failure
  - bisphosphonate therapy
  - uncontrolled hypertension at the screening visit (blood pressure > 150/90 mmHg despite use of four agents), unless evidence available from home or 24-hour blood pressure monitoring that blood pressure is usually controlled
  - participation in another clinical trial (not including observational studies and registries) concurrently or within 30 days prior to screening for entry into this trial
  - known allergy to sodium bicarbonate tablets or lactose.

Trial intervention and comparator

The trial intervention was oral sodium bicarbonate tablets. Each tablet contained 500 mg of sodium bicarbonate (equivalent to 6 mmol of sodium and 6 mmol of bicarbonate). The initial dose dispensed was one tablet three times per day. If the serum bicarbonate level was still < 22 mmol/l at 3 months, the dose was increased to two tablets three times per day for the remaining duration of participation. The comparator was matching placebo tablets. No specific measures were used to enhance adherence beyond reminding participants to take their medication at each study contact.

Outcome measures

Primary outcome

The primary outcome for the trial was the between-group difference in the Short Physical Performance Battery (SPPB) score at 12 months, adjusted for baseline values. The SPPB is a test of lower limb strength and balance.[37] It comprises three tests: a balance test (tandem balance, semi-tandem balance and single leg balance), a timed sit to stand from a chair five times, and gait speed over a 4-m course. The test is scored from 0 (worst score; includes those who cannot perform any component) to 12 (best score). The SPPB is a robust predictor of a range of adverse outcomes in older people, including death, dependency and future disability.[38,39]

Secondary outcomes

Table 1 lists the secondary outcomes measured in the trial and their time points, encompassing a range of measures of physical function, anthropometry, quality of life, vascular health and bone health. For all secondary outcomes, data from all available time points were used in repeated-measures analyses. Repeated-measures evaluation of the SPPB score (in contrast to the 12-month primary outcome measure) was therefore a secondary outcome. Details of the methods used for outcomes measurement and analysis are provided in *Appendix 3*.

Health economic outcomes

Data on primary care and secondary care (inpatient and outpatient) use were captured by questionnaire at each study visit to inform the health economic analysis. Participants were asked to recall their frequency of service use over the previous month at each follow-up point. Service use included hospital admissions, day case visits, outpatient clinic visits, day hospital visits, other health-care professionals visits [general practitioner (GP), district nurse, physiotherapist, occupational therapist, speech therapist] and other social care visits (day centre and home helper/carer). National published sources were used to value the resources used (see *Appendix 4*) and the sum of these responses was used to calculate annual costs for the first and second year of follow-up. To assess outcomes, the EuroQoL 5-Dimensions, three-level version (EQ-5D-3L), Investigating Choice Experiments for the preferences of older people CAPability - older people (ICECAP-O) and global life satisfaction measures were used.

Sample size calculation

We based the original sample size calculation on the ability to detect a 1-point difference in the SPPB score (i.e. the primary outcome). This difference has been proposed as the minimum clinically important difference (MCID) by previous investigators.[37] Previous work with older people showed a standard deviation of 2.6 for the SPPB. To detect a 1-point difference between groups at 12 months given this standard deviation would require 143 participants per group, given a two-sided alpha of 0.05 and power of 90%.

To ensure that the trial had sufficient power for the key secondary outcome of health-related quality of life, we also estimated the sample size required to detect the MCID for the EuroQol-5 Dimensions (EQ-5D) measure. For the EQ-5D, the MCID is 0.074.[46] To detect this with a two-sided alpha of 0.05 and power of 90%, assuming a standard deviation of change of 0.2, as found in our previous studies,[47,48] would require 154 participants per group.

Assuming a 10% loss to follow-up every 6 months (based on previous medication trials in frail older people[47,49]), we estimated that we would require 380 participants (190 per group) to ensure adequate power for the primary outcome and the EQ-5D outcome at 12 months.

TABLE 1 List of secondary outcomes in the BiCARB trial

Test	Time points measured
Physical function and anthropometry	
6-minute walk distance[40]	0, 3, 6, 12 and 24 months
Handgrip strength[41]	0, 3, 6, 12 and 24 months
Weight	0, 3, 6, 12 and 24 months
Mid-arm muscle circumference[42]	0, 3, 6, 12 and 24 months
Triceps skinfold thickness[42]	0, 3, 6, 12 and 24 months
Mid-thigh circumference[42]	0, 3, 6, 12 and 24 months
Health-related quality of life	
EQ-5D-3L score[43]	0, 3, 6, 12 and 24 months
EQ-5D thermometer[43]	0, 3, 6, 12 and 24 months
KDQoL questionnaire[44]	0, 3, 6, 12 and 24 months
ICECAP-O questionnaire[45]	0, 3, 6, 12 and 24 months
Renal function	
Creatinine and eGFR	0, 3, 6, 12 and 24 months
Cystatin C	0, 3, 6, 12 and 24 months
Urinary albumin-to-creatinine ratio	0, 3, 6, 12 and 24 months
Bone and mineral metabolism	
Tartrate-resistant acid phosphatase-5b	0, 12 and 24 months
Bone-specific alkaline phosphatase	0, 12 and 24 months
PTH	0, 12 and 24 months
25-hydroxyvitamin D and 1,25 dihydroxyvitamin D	0, 12 and 24 months
Serum calcium and serum phosphate	0, 3, 6, 12 and 24 months
Vascular risk markers	
N-terminal pro-B-type natriuretic peptide	0, 12 and 24 months
Systolic and diastolic blood pressure	0, 3, 6, 12 and 24 months
Total cholesterol	0, 3, 6, 12 and 24 months
Other biochemistry	
Thyroid-stimulating hormone	0, 3, 6, 12 and 24 months
Serum potassium, serum albumin, serum bicarbonate	0, 3, 6, 12 and 24 months
Haemoglobin	0, 3, 6, 12 and 24 months
Glycosylated haemoglobin (HbA_{1c})	0, 3, 6, 12 and 24 months

EQ-5D, EuroQoL 5-Dimensions; EQ-5D-3L, EuroQoL 5-Dimensions, three-level version; KDQoL, Kidney Disease Quality of Life.

Chapter 3 Methods

Regulatory approvals

The BiCARB trial was a Clinical Trial of an Investigational Medicinal Product (CTIMP). As such, the trial was subject to approval and oversight from the Medicines and Healthcare products Regulatory Authority (EudraCT number 2011-005271-16; Clinical Trial Authorisation number 41692/0001/001-0001). Ethics approval was granted by the East of Scotland NHS Research Ethics Committee (reference number 12/ES/0023). The trial was co-sponsored by the University of Dundee and NHS Tayside (Tayside Academic Health Sciences Collaboration). The trial was registered at www.isrctn.com with the identifier ISRCTN09486651.

Participants

Site participation

At the trial planning stage, six core sites were selected (Dundee, Aberdeen, Salford, Sheffield, Canterbury and Guy's/St Thomas'). Early in the course of the trial, the decision was taken to recruit from a much larger number of sites to address issues of slow recruitment rates; potential sites were approached through the NIHR Renal Clinical Research Network. Sites were selected on the basis of willingness to participate, access to a local investigator with appropriate Good Clinical Practice (GCP) training and sufficient nephrology colleagues at the site with clinical equipoise on the trial intervention to support randomising participants rather than immediately commencing oral bicarbonate therapy.

Participant identification

Participants were identified through secondary care services, either by screening attendees at clinics (predominantly renal clinics, including low-clearance clinics) or by searching local renal and biochemistry databases. At two sites (Dundee and Aberdeen), participants were also sought through searches of primary care records. Initial searches focused on identifying patients with CKD category 4 or 5 who were not on dialysis and who had historical serum bicarbonate concentrations of < 22 mmol/l.

Recruitment process

Potentially eligible participants were given information about the study. The participant information sheet is available in *Report Supplementary Material 3*. Participants were invited to attend a screening visit. After obtaining written informed consent, medical history and medication use were recorded to check for exclusion criteria. If creatinine and bicarbonate results were available within the previous month, these values were used to determine eligibility. If these results were not available, a screening blood sample was taken to measure the creatinine concentration, derive the eGFR (according to the MDRD4 equation) and measure the serum bicarbonate concentration.

Participants found to be eligible at the screening visit underwent the baseline study assessments either on the same day (if historical blood results were available) or at a separate visit (if screening bloods were used).

Washout arrangements

For potentially eligible participants already taking oral sodium bicarbonate who wished to participate, consent was obtained and a 3-month washout period instituted. After the washout period, the screening visit was performed and only those participants fulfilling the eligibility criteria at the screening visit proceeded to the baseline assessment and randomisation.

Randomisation and treatment allocation

Randomisation was performed using an interactive web-based randomisation, drug assignment and inventory management system [Tayside Randomisation SysTem (TRuST)] run by the Health Informatics Centre, University of Dundee. The system was run independently of the research team to preserve allocation concealment. Randomisation was performed in a 1 : 1 ratio, stratified by site, and employed a minimisation algorithm to balance male versus female sex, CKD category 4 versus category 5, and age < 75 years versus ≥ 75 years.

Participants were allocated study medication bottles (one bottle per month) containing either 500-mg sodium bicarbonate tablets or matching placebo tablets; bottles were allocated based on bottle identification numbers generated by the TRuST randomisation system.

Unmasking

The treatment code was broken only when the clinical team treating a participant deemed knowledge of treatment allocation to be essential for management of the participant. Unmasking was performed by the clinical trials pharmacist at Dundee using the TRuST system. The pharmacist was contactable via a 24-hour hotline. After unmasking, TRuST automatically informed the trial team of the unmasking event without disclosing the treatment allocation. No tests for the success of masking (e.g. asking trial personnel to guess which group participants were allocated to) were performed.

Intervention and comparator

The trial intervention consisted of either 500-mg sodium bicarbonate tablets or matching placebo tablets (containing lactose and microcrystalline cellulose). Active and placebo tablets were manufactured and bottled by Legosan AB (Kumla, Sweden). Bottles were imported to the UK via Tayside Pharmaceuticals (Dundee, UK), which undertook quality testing and qualified person release and distributed bottles to participating sites. Study medications were held at site pharmacies under temperature-controlled conditions prior to dispensing to participants. For the first 3 months of participation, participants were instructed to take one tablet three times per day.

Uptitration

Uptitration took place in a double-dummy fashion. Serum bicarbonate concentrations were measured at the 3-month visit. Participants with a serum bicarbonate concentration of < 22 mmol/l were instructed to increase their intake of study medication to two tablets three times per day. Participants with a serum bicarbonate concentration of ≥ 22 mmol/l were instructed to continue taking one tablet three times per day for the remainder of their time in the trial.

Returned medication and tablet counting

At each visit, unused tablets were returned by participants, counted and entered into the study database to allow adherence to be calculated.

Outcomes measurement

Outcomes were measured at baseline and at 3, 6, 12 and 24 months. Outcomes were collected by research nurses at each site, who were masked to treatment allocation. *Figure 1* shows the study processes at each visit, from screening to the end of trial participation.

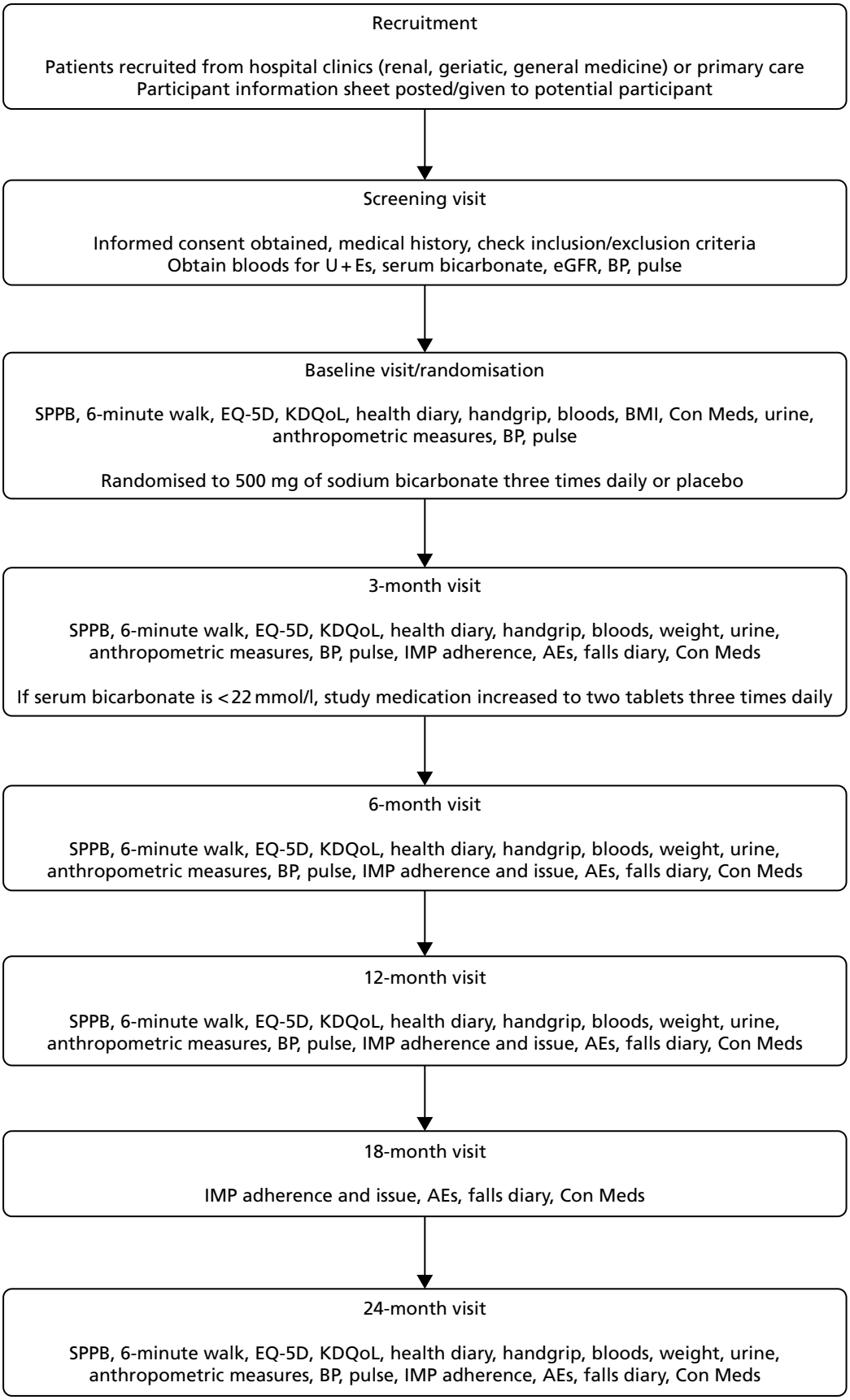

FIGURE 1 Flow of participant visits and activities through the trial. AE, adverse event; BMI, body mass index; BP, blood pressure; Con Meds, concomitant medications; IMP, Investigational Medicinal Product; KDQoL, Kidney Disease Quality of Life; U+Es, urea and electrolytes.

Data management

Trial data were collected onto paper case report forms and then entered onto a trial-specific database built using OpenClinica software V3.1.2 (OpenClinica LLC, Waltham, MA, USA). Participants were identified using a unique study identifier and data were stored on a secure, backed-up, University of Dundee server system. Source data verification was conducted for all randomised participants for age, sex, inclusion and exclusion criteria, laboratory values analysed as part of routine clinical practice, baseline medications and adverse events. Batch validation and database audit procedures were run as outlined in the trial Data Management Plan. Target error rates for the primary outcome and adverse events were set at < 0.5% and for other audited fields were set at < 2%, with corrections made until error rates fell within these limits.

Safety reporting

All adverse events (serious and non-serious) were collected at each site using adverse event logs. Adverse events were coded centrally by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 16.1 (www.meddra.org). Given the anticipated high frequency of adverse events in this study population, serious adverse events were collected but not reported to the trial sponsor or to the regulatory authority (Medicines and Healthcare products Regulatory Agency) if they fell into the following categories:

- any new cardiovascular event
- any new diagnosis or treatment of cancer
- any death or hospitalisation as a result of a fall or fracture
- any death or hospitalisation as a result of infection
- any death or hospitalisation as a result of exacerbation of an existing medical condition
- any admission for elective or planned investigation or treatment
- death, admission or treatment for deteriorating renal function or high or low potassium concentrations.

All adverse events (including those in the above list) were presented to the independent Data Monitoring Committee (DMC) classified by MedDRA System Organ Class; prespecified outcomes of particular interest (death, worsening heart failure, fluid overload or breathlessness) were also presented. All adverse events are included in the analysis reported here.

Trial oversight committees

An independent DMC met every 6 months. The DMC comprised an experienced trials biostatistician, an academic geriatrician and an academic nephrologist. The DMC had access to unblinded data on baseline participant characteristics and adverse events. The DMC reported to the chairperson of the independent Trial Steering Committee (TSC); members were appointed by the NIHR and operated under an agreed charter.

The independent TSC was appointed by the NIHR and was chaired by an experienced triallist specialising in geriatric medicine. Other independent members of the TSC were an academic nephrologist, an academic geriatrician and a lay member with personal experience of kidney disease. The TSC met at least every 6 months over the course of the trial; additional meetings were held as required for timely decision-making. The TSC chairperson reported to the project manager at the NIHR by letter and provided minutes after each TSC meeting; the TSC also operated under an agreed charter.

Day-to-day management of the trial was performed by the Trial Management Group (TMG), comprising the lead applicant, co-applicants and Tayside Clinical Trials Unit (CTU) staff. Local investigators and research nurses at each site were invited to join all TMG meetings, which took place monthly until the end of recruitment and then every 2 months until the end of the grant funding period. Monthly teleconferences between the trial manager and research nurses were used to share best recruitment practice and to troubleshoot trial processes.

Patient and public involvement

A patient representative formed part of the independent TSC and had input into the conduct of the trial, including making significant changes to the protocol; this representative also reviewed the final results. The study design and outcome measures were discussed with a panel of older people at the design stage of the trial, who provided advice and feedback.

Important changes to the trial design and conduct after trial commencement

Several significant changes were made to the conduct of the trial after commencement, mostly in response to the slow recruitment rates:

- The number of sites planned was originally six; this was expanded to 27 to address the slow recruitment rates.
- A substudy at two sites (Dundee and Aberdeen) was originally planned to examine bone mineral density by dual-energy X-ray absorptiometry (DEXA) and vascular stiffness by applanation tonometry. These substudies were discontinued because of poor recruitment rates, with only two participants undergoing the substudy measurements.
- The exclusion criteria were relaxed early in the recruitment phase following a review of reasons for non-recruitment. Changes were made to reduce the lower age limit from 65 to 60 years, to allow the inclusion of those taking calcium acetate or sevelamer and to allow the inclusion of those with hypertension controlled according to home monitoring despite high office blood pressure readings. Both of the phosphate binders, calcium acetate and sevelamer, are routinely used alongside bicarbonate in clinical practice and home monitoring of blood pressure is increasingly used in clinical practice to determine the adequacy of blood pressure control. These changes were therefore deemed not to compromise the safety or scientific integrity of the trial but likely to enhance the generalisability of the results by expanding the pool of eligible participants. In addition, provision was made to include patients currently taking sodium bicarbonate if they underwent a 3-month washout period.
- The TSC took the decision, in conjunction with the funder, to stop recruitment once 300 of the original target of 380 participants had been randomised. This decision was taken in view of the slowing recruitment rates; the sample size calculations were revisited prior to this decision being taken, as discussed in *Re-estimation of the sample size*.
- The TSC took the decision, in conjunction with the funder, to truncate follow-up once all participants had reached the primary outcome point of 12 months. This decision was taken to enable a prompt conclusion to the trial so that the results could be disseminated in a timely fashion; it was not based on an interim analysis of the results. A small number of individuals did not therefore progress to the 24-month follow-up point.
- Two extensions to the recruitment time were granted by the NIHR to compensate for the slower than anticipated recruitment rates.

Re-estimation of the sample size

To inform the decision on whether or not to terminate recruitment once 300 participants had been randomised, a revised sample size calculation was prepared by the research team and was considered by the TSC. This calculation was carried out without knowledge of treatment allocation or any follow-up data beyond baseline values and standard deviations for the trial population.

The revised sample size calculation assumed the use of a mixed-model repeated-measures analysis with two time points (12-month follow up and baseline), a standard deviation of 2.6 for the primary outcome of SPPB score, an attrition rate of 30% by 12 months and an alpha of 0.05. Assuming a within-person correlation of 0.7, 300 participants would give 85% power to detect a 1-point difference in SPPB score between groups (the MCID) at 12 months. Assuming a within-person correlation of 0.6, the same sample size would give 87% power to detect this difference.

Based on these revised power estimates, the TSC recommended that recruitment stop at 300 participants, as sufficient power to detect the MCID for the primary outcome would still be present and continuing recruitment would risk greatly prolonging the trial with little benefit in terms of statistical power.

Statistical analysis

A prespecified statistical analysis plan (SAP) was drafted, reviewed by the TMG and the independent TSC and signed off before the last visit of the last participant (see *Report Supplementary Material 2*).

The primary outcome (between-group difference in SPPB score at 12 months) was analysed using linear mixed models, adjusted for baseline measurements, minimisation variables (age, sex and stage of CKD) and a random effect variable for recruitment site. Prespecified subgroup analyses for the primary outcome were conducted (SPPB $\geq$ 10 points vs. < 10 points, CKD category 4 vs. category 5, age < 75 vs. $\geq$ 75 years, male vs. female, baseline bicarbonate < 18 mmol/l vs. $\geq$ 18 mmol/l). These factors were selected as being both of clinical interest and likely to be related to the primary outcome based on previous work. Sensitivity analyses were planned for > 80% versus $\leq$ 80% adherence, exclusion of those undergoing washout prior to randomisation and using multiple imputation for missing data. Multiple imputation was performed with SAS® PROC MI v9.4 (SAS Institute Inc., Cary, NC, USA) using a Markov chain Monte Carlo method with multiple chains over 1000 iterations (SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc. in the USA and other countries. ® indicates USA registration). Predictor variables were visit, sex, age group, CKD stage and practice.

Secondary outcomes were analysed using repeated-measures models, adjusted for baseline values and minimisation variables as above. Time-to-event analyses (time to death, time to commencing renal replacement therapy) were conducted using Cox proportional hazards models adjusted for minimisation variables as above. For all analyses, a two-sided *p*-value of < 0.05 was taken as significant, with no adjustment for multiple testing. Analyses were performed using SAS v9.4 software. Unmasking of randomisation groups was performed only after completing the statistical analysis.

Health economic analysis

A prespecified health economic analysis plan was also drafted, reviewed by the TMG and signed off before the last visit of the last participant (see *Report Supplementary Material 1*).

The primary aim was to assess the cost-effectiveness of the addition of bicarbonate therapy relative to placebo from the perspective of the UK health and social care system. A cost–utility analysis was undertaken that involved estimation of the incremental costs and incremental effects [effectiveness was measured using quality-adjusted life-years (QALYs), based on responses to the EQ-5D-3L instrument]. Estimation was performed using generalised linear regression modelling, with adjustment for skewed data and for baseline differences in cost, EQ-5D-3L values and other patient characteristics (age, sex, stage of CKD). Non-parametric bootstrap methods[50] were used for calculating CIs around cost and QALY differences. Cost-effectiveness acceptability curves were employed to show the probability that bicarbonate therapy was cost-effective for different values of willingness to pay per additional QALY.[51]

Chapter 4 Clinical effectiveness results

Recruitment

A total of 300 participants were randomised into the trial between May 2013 and February 2017. *Appendix 5* shows the cumulative recruitment per month throughout the trial recruitment phase (see *Figures 26* and *27*) and recruitment by site (see *Table 23*). Following discussion between the trial team, the independent DMC and TSC and the funder, recruitment was terminated at the end of February 2017 because of the very low ongoing recruitment rates. As part of this decision-making process, revised sample size/power calculations indicated that, under the proposed analysis method for the primary outcome, the trial had 87% power to detect the MCID with the recruited sample size.

Flow of participants through the trial

Figure 2 shows the flow of participants through the trial, using the format recommended by the Consolidated Standards of Reporting Trials (CONSORT).[52] Dropout rates were similar in both arms at each time point, but overall dropout rates were slightly higher than anticipated (18% at 6 months and 27% at 12 months). Once all participants had completed their 12-month (primary outcome) visit, the TSC recommended that further follow-up for the last 40 participants be truncated; the last patient visit occurred in February 2018. These participants did not therefore progress to their 18-month or 24-month visit and thus dropout after 12 months appears artefactually higher. Only four participants underwent the 3-month washout option prior to the screening visit.

Participant baseline characteristics

Participant baseline characteristics are presented in *Table 2*. The two groups were well balanced for most key baseline characteristics, including aetiology of renal dysfunction.

Adherence and effect of the intervention on serum bicarbonate levels

Data on adherence to the study medication are shown in *Table 3*. The adherence rate was moderate, with approximately 50% in both arms exceeding the threshold of 80% commonly used to denote good adherence. The mean prescribed dose of bicarbonate in the bicarbonate arm across the whole follow-up period was 1.88 g per day (compared with a maximum possible dose of 3 g per day) and the mean ingested dose of bicarbonate in the bicarbonate arm across the whole follow-up period was 1.39 g per day.

A modest but significant increase in serum bicarbonate concentration was seen in the intervention arm by 3 months; this difference attenuated with time and was no longer significant by 24 months, as shown in *Figure 3*. The treatment effect of bicarbonate supplementation across the whole follow-up period was 1.1 mmol/l (95% CI 0.6 to 1.6 mmol/l; $p < 0.001$); bicarbonate levels at each follow-up time point are shown later in this chapter (see *Table 7*).

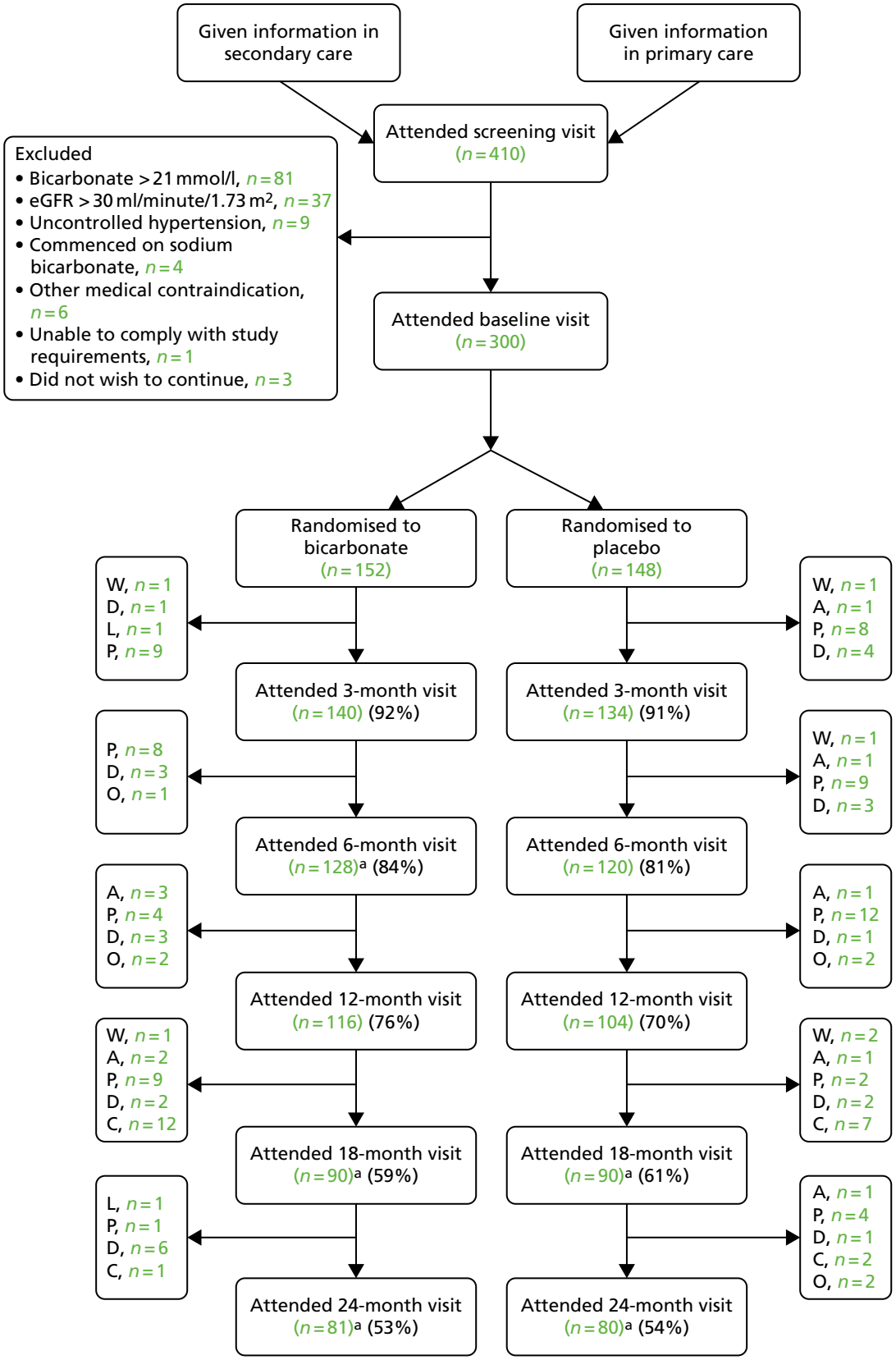

FIGURE 2 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. a, Some did not attend visit but had not dropped out. A, withdrew because of adverse event; C, early study completion because of truncated follow-up; D, died; L, lost to follow-up; O, other; P, participant chose to withdraw; W, withdrawn by investigator.

TABLE 2 Baseline characteristics of randomised participants ($n = 300$)

Characteristic	Randomised group	
	Bicarbonate ($N = 152$)	Placebo ($N = 148$)
Mean (SD) age (years)	73.9 (7.6)	74.0 (6.6)
Aged 60–69 years, *n* (%)	57 (37.5)	35 (23.6)
Aged 70–79 years, *n* (%)	53 (34.9)	81 (54.7)
Aged ≥ 80 years, *n* (%)	42 (27.6)	32 (21.6)
Female sex, *n* (%)	42 (27.6)	44 (29.7)
Ethnicity, *n* (%)		
White	144 (94.7)	143 (96.6)
East Asian	0 (0)	1 (0.7)
Black	1 (0.7)	0 (0)
South Asian	4 (2.6)	2 (1.4)
Hispanic	1 (0.7)	0 (0)
Other	2 (1.3)	2 (1.4)
Cause of renal dysfunction, *n* (%)		
Hypertension	37 (24.3)	40 (27.0)
Diabetes mellitus	23 (15.1)	23 (15.5)
Glomerulonephritis	9 (5.9)	11 (7.4)
Polycystic kidney disease	11 (7.2)	9 (6.1)
Vascular disease	19 (12.5)	21 (14.2)
Other	52 (34.2)	63 (42.6)
Not known	31 (20.4)	22 (14.9)
Cardiovascular comorbidity, *n* (%)		
Hypertension	135 (88.8)	129 (87.2)
Diabetes mellitus	54 (35.5)	47 (31.8)
Ischaemic heart disease	26 (17.1)	31 (20.9)
Stroke	16 (10.5)	12 (8.1)
Heart failure	19 (12.5)	5 (3.4)
Peripheral vascular disease	14 (9.2)	10 (6.8)
Previous fragility fracture, *n* (%)	2 (1.3)	5 (3.4)
Mean (SD) number of medications, *n* (%)	8.2 (3.7)	7.9 (3.3)
Medication use, *n* (%)		
ACEi/ARB	105 (69.1)	91 (61.5)
Phosphate binder	32 (21.1)	28 (18.9)
Activated vitamin D	77 (50.7)	73 (49.3)
Erythropoietin	89 (58.6)	106 (71.6)
Iron	60 (39.5)	51 (34.5)
Mean (SD) eGFR (ml/minute/1.73 m^2)	19.7 (6.5)	18.2 (6.4)
CKD category 5 (%)	48 (32.4)	34 (22.4)
Mean (SD) serum bicarbonate concentration (mmol/l)	20.6 (2.6)	20.1 (2.5)
Mean (SD) haemoglobin concentration (g/l)	115 (14)	117 (17)
Mean (SD) serum potassium concentration (mmol/l)	4.9 (0.5)	4.9 (0.5)
Mean (SD) SPPB score	8.0 (2.4)	8.1 (2.2)
Mean (SD) 6-minute walk distance (m)	304 (134)	317 (133)

continued

TABLE 2 Baseline characteristics of randomised participants ($n = 300$) (*continued*)

Characteristic	Randomised group	
	Bicarbonate ($N = 152$)	Placebo ($N = 148$)
Mean (SD) handgrip strength (kg)		
Men	26.6 (8.8)	28.0 (7.6)
Women	15.4 (4.8)	15.8 (4.4)
Mean (SD) body mass index (kg/m^2)	28.9 (4.5)	28.3 (4.6)
Mean (SD) mid-arm muscle circumference (cm)	24.9 (3.6)	24.8 (4.0)
Mean (SD) triceps skinfold thickness (mm)	16 (8)	17 (9)
Mean (SD) mid-thigh circumference (cm)	47.4 (7.0)	46.8 (7.0)
Mean (SD) EQ-5D-3L score	0.73 (0.22)	0.74 (0.24)
Mean (SD) EQ-5D thermometer score	69 (19)	71 (19)
Mean (SD) KDQoL scores		
SF-36 PCS	36 (11)	36 (11)
SF-36 MCS	53 (11)	54 (9)
Burden	75 (26)	75 (25)
Symptoms	79 (14)	81 (12)
Effects	86 (14)	87 (15)
Mean (SD) office systolic blood pressure (mmHg)	143 (18)	143 (18)
Mean (SD) office diastolic blood pressure (mmHg)	75 (11)	73 (10)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; KDQoL, Kidney Disease Quality of Life; MCS, mental component score; PCS, physical component score; SD, standard deviation; SF-36, Short Form questionnaire-36 items.

TABLE 3 Intervention uptitration and adherence

Characteristic	Randomised group, *n* (%)	
	Bicarbonate ($N = 152$)	Placebo ($N = 148$)
3-month visit		
500 mg three times per day	82 (53.9)	45 (30.4)
1000 mg three times per day	46 (30.3)	83 (56.1)
Not dispensed	12 (7.9)	6 (4.1)
Dropped out before 3-month visit	12 (7.9)	8 (5.4)
Adherence (%) (SD)	72.8 (35.2)	73.4 (39.6)
Adherence $\leq$ 80% (%)	76 (50.0)	73 (49.3)

SD, standard deviation.

Primary outcome

Table 4 shows the primary outcome analysis: the difference in SPPB score at 12 months between groups. No significant effect of bicarbonate treatment was seen on the primary outcome (treatment effect –0.4 points, 95% CI –0.9 to 0.1 points; $p = 0.15$); analysis adjusted only for baseline SPPB score and analyses adjusted for baseline SPPB score, age, sex and CKD category gave the same result. Multiple imputation to account for missing data gave similar results (treatment effect –0.3 points, 95% CI –1.0 to 0.3 points; $p = 0.29$). As only four participants underwent the washout period prior to randomisation, the sensitivity analysis excluding this subgroup was not conducted.

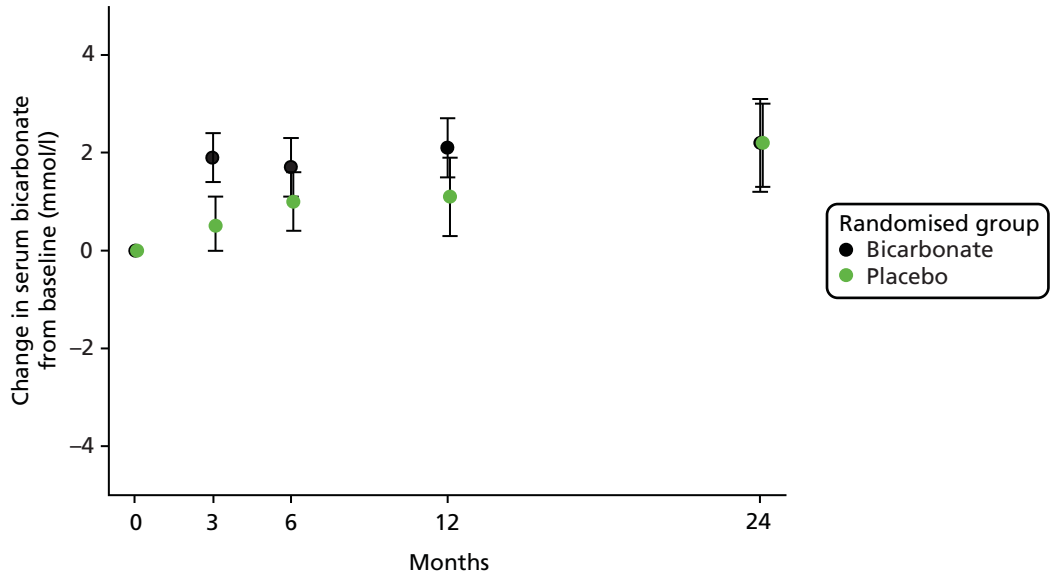

FIGURE 3 Change in bicarbonate concentration relative to baseline.

TABLE 4 Primary outcome: SPPB score (points) at 12 months

Time point	Randomised group, mean (SD)		Adjusted treatment effect[a] (95% CI)	*p*-value
	Bicarbonate	Placebo		
Baseline	8.0 (2.4) (*n* = 140)	8.1 (2.2) (*n* = 134)	–0.4 (–0.9 to 0.1)	0.15
12 months	8.3 (2.5) (*n* = 97)	8.8 (2.2) (*n* = 90)		

SD, standard deviation.
a Adjusted for baseline SPPB score, age, sex and CKD category (4 vs. 5).

Subgroup analyses

No significant interaction was seen in subgroup analyses (age, sex, CKD category, high vs. low baseline bicarbonate concentration, high vs. low baseline SPPB score), with all subgroups showing similar effect sizes for the primary outcome; all tests for interactions were non-significant. Details are presented in *Figure 4*.

Effect of adherence on the primary outcome

A further preplanned subgroup analysis was conducted, comparing the primary outcome treatment effect for those with good adherence (defined a priori as > 80%) with the treatment effect for those with poorer adherence (defined a priori as ≤ 80%). Those with good adherence showed an adjusted treatment effect at 12 months of –0.6 points (95% CI –1.4 to 0.1 points; $p = 0.07$), whereas those with poorer adherence showed an adjusted treatment effect of 0.0 points (95% CI –0.7 to 0.7 points; $p = 0.97$). The difference in treatment effect was not significant (*p*-value for interaction = 0.27).

Secondary outcomes

Physical function

Repeated-measures analysis showed that the SPPB score was slightly worse in the bicarbonate arm than in the placebo arm. Similarly, 6-minute walk distance and grip strength showed an adverse effect of treatment on repeated-measures analyses. Details are presented in *Table 5*.

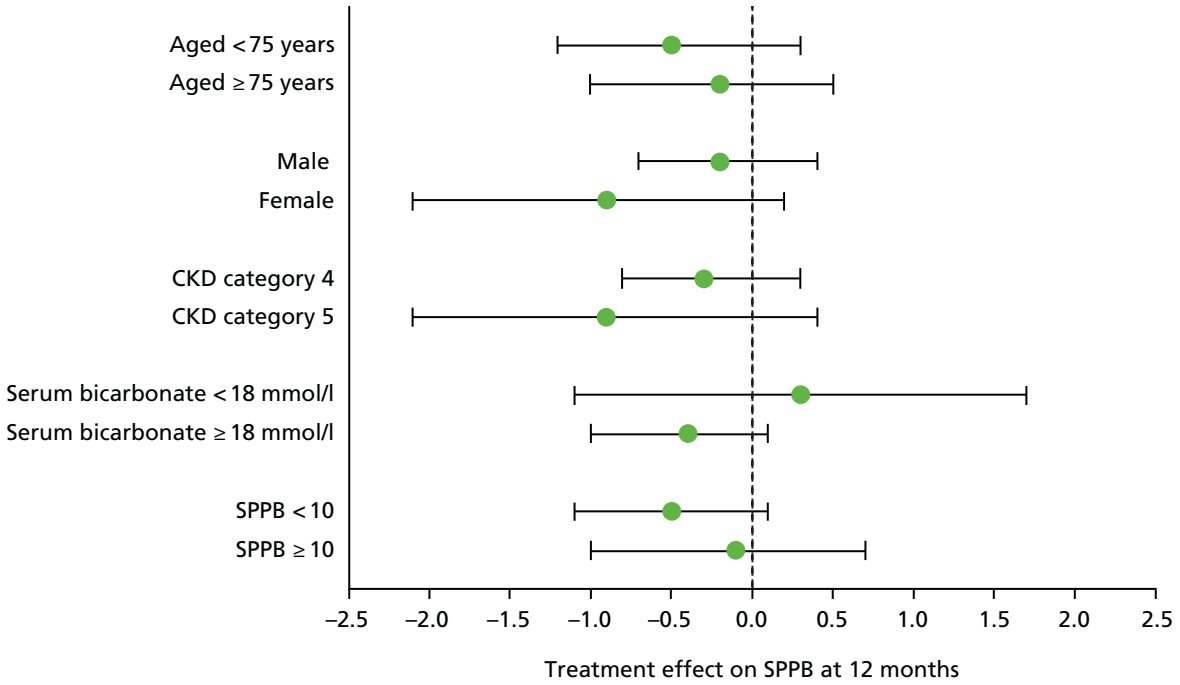

FIGURE 4 Subgroup analyses for the primary outcome.

TABLE 5 Secondary outcomes: measures of physical function and anthropometry

Outcome	Time point	Randomised group, mean (SD)		Treatment effect (95% CI)	*p*-value
		Bicarbonate	Placebo		
SPPB score (points)	Baseline	8.0 (2.4) (*n* = 140)	8.1 (2.2) (*n* = 134)	–0.6 (–1.0 to –0.1)	0.02
	3 months	8.2 (2.2) (*n* = 120)	8.7 (2.3) (*n* = 123)		
	6 months	8.2 (2.5) (*n* = 113)	8.9 (2.6) (*n* = 111)		
	12 months	8.3 (2.5) (*n* = 97)	8.8 (2.2) (*n* = 90)		
	24 months	7.7 (2.5) (*n* = 72)	8.7 (2.5) (*n* = 73)		
6-minute walk distance (m)	Baseline	304 (134) (*n* = 151)	317 (133) (*n* = 148)	–33 (–62 to –4)	0.02
	3 months	308 (143) (*n* = 134)	333 (131) (*n* = 128)		
	6 months	307 (151) (*n* = 127)	334 (147) (*n* = 114)		
	12 months	294 (162) (*n* = 109)	336 (154) (*n* = 101)		
	24 months	300 (167) (*n* = 80)	327 (184) (*n* = 79)		
Grip strength (kg)	Baseline	Men: 26.6 (8.8) (*n* = 110); women: 15.4 (4.8) (*n* = 42)	Men: 28.0 (7.6) (*n* = 104); women: 15.8 (4.4) (*n* = 44)	–1.5 (–2.8 to –0.2)	0.03
	3 months	Men: 26.5 (7.1) (*n* = 103); women: 15.8 (4.8) (*n* = 35)	Men: 27.5 (7.9) (*n* = 95); women: 16.3 (4.1) (*n* = 37)		
	6 months	Men: 26.3 (7.1) (*n* = 97); women: 15.1 (4.7) (*n* = 31)	Men: 28.3 (7.2) (*n* = 83); women: 16.6 (4.9) (*n* = 33)		
	12 months	Men: 25.9 (7.2) (*n* = 85); women: 15.2 (5.2) (*n* = 27)	Men: 28.4 (7.9) (*n* = 72); women: 15.5 (4.1) (*n* = 30)		
	24 months	Men: 25.5 (8.3) (*n* = 57); women: 14.1 (5.5) (*n* = 23)	Men: 28.7 (7.3) (*n* = 56); women: 15.1 (3.6) (*n* = 23)		

TABLE 5 Secondary outcomes: measures of physical function and anthropometry (*continued*)

Outcome	Time point	Randomised group, mean (SD)		Treatment effect (95% CI)	*p*-value
		Bicarbonate	Placebo		
Weight (kg)	Baseline	82.3 (16.9) (*n* = 152)	81.5 (15.9) (*n* = 148)	0.2 (–2.9 to 3.4)	0.89
	3 months	83.0 (16.7) (*n* = 137)	82.2 (15.4) (*n* = 131)		
	6 months	83.1 (16.7) (*n* = 127)	81.1 (14.5) (*n* = 117)		
	12 months	83.4 (16.3) (*n* = 112)	81.1 (14.6) (*n* = 102)		
	24 months	80.1 (14.5) (*n* = 81)	80.9 (14.6) (*n* = 79)		
Mid-arm muscle circumference (cm)	Baseline	24.9 (3.6) (*n* = 150)	24.8 (4.0) (*n* = 147)	0.0 (–0.6 to 0.6)	0.99
	3 months	24.9 (3.5) (*n* = 136)	25.2 (4.3) (*n* = 131)		
	6 months	25.1 (4.3) (*n* = 126)	24.8 (4.1) (*n* = 115)		
	12 months	25.2 (3.2) (*n* = 112)	24.4 (3.8) (*n* = 100)		
	24 months	24.2 (3.5) (*n* = 78)	24.9 (3.2) (*n* = 77)		
Triceps skinfold thickness (mm)	Baseline	16 (8) (*n* = 151)	17 (9) (*n* = 148)	–1 (–2 to 1)	0.34
	3 months	17 (9) (*n* = 138)	17 (8) (*n* = 131)		
	6 months	15 (7) (*n* = 126)	17 (9) (*n* = 116)		
	12 months	16 (10) (*n* = 111)	17 (8) (*n* = 100)		
	24 months	15 (6) (*n* = 77)	16 (8) (*n* = 79)		
Mid-thigh circumference (cm)	Baseline	47.4 (7.0) (*n* = 146)	46.8 (7.0) (*n* = 143)	0.1 (–0.8 to 1.1)	0.80
	3 months	46.7 (6.7) (*n* = 133)	46.7 (6.9) (*n* = 129)		
	6 months	46.8 (5.4) (*n* = 128)	48.3 (13.4) (*n* = 112)		
	12 months	46.5 (6.2) (*n* = 108)	45.7 (6.7) (*n* = 99)		
	24 months	46.5 (5.2) (*n* = 79)	46.4 (4.7) (*n* = 78)		

SD, standard deviation.
Repeated-measures analysis of variance adjusted for baseline values, age, sex and CKD category.

Anthropometry

No significant difference between groups was seen on repeated-measures analysis for weight, triceps skinfold thickness, mid-thigh circumference or mid-arm muscle circumference (see *Table 5*).

Quality of life

Both the health state and thermometer scores from the EQ-5D general health-related quality of life tool showed an adverse effect of treatment on repeated-measures analysis, but this did not reach statistical significance. There were no significant differences between groups in the disease-specific quality of life domains from the Kidney Disease Quality of Life (KDQoL) questionnaire, but the mental health component summary of the Short Form questionnaire-36 items (SF-36) (part of the KDQoL questionnaire) was significantly worse in the bicarbonate arm than in the placebo arm. Details are presented in *Table 6*.

Renal function

No significant treatment effect was seen on renal function between the bicarbonate arm and the treatment arm on repeated-measures analysis; this was consistent whether using serum creatinine concentration, eGFR derived from serum creatinine or serum cystatin C concentration as alternative markers of renal function. There was also no significant treatment effect between arms on the urinary albumin-to-creatinine ratio. Details are presented in *Table 7*. For those remaining under follow-up in the trial, the rates of decline in eGFR were low, as shown in *Figure 5*.

TABLE 6 Secondary outcomes: measures of quality of life

Outcome	Time point	Randomised group, mean (SD)		Treatment effect (95% CI)	*p*-value
		Bicarbonate	Placebo		
EQ-5D-3L score	Baseline	0.728 (0.220) (*n* = 143)	0.739 (0.240) (*n* = 137)	–0.039 (–0.079 to 0.001)	0.06
	3 months	0.706 (0.220) (*n* = 132)	0.759 (0.212) (*n* = 123)		
	6 months	0.707 (0.209) (*n* = 120)	0.768 (0.172) (*n* = 108)		
	12 months	0.699 (0.231) (*n* = 105)	0.774 (0.165) (*n* = 94)		
	24 months	0.715 (0.243) (*n* = 70)	0.751 (0.188) (*n* = 71)		
EQ-5D thermometer score	Baseline	69 (19) (*n* = 146)	71 (19) (*n* = 137)	–3 (–7 to 1)	0.09
	3 months	68 (19) (*n* = 134)	70 (18) (*n* = 122)		
	6 months	67 (20) (*n* = 116)	73 (16) (*n* = 110)		
	12 months	67 (19) (*n* = 106)	71 (17) (*n* = 91)		
	24 months	68 (20) (*n* = 73)	70 (18) (*n* = 72)		
KDQoL: symptoms	Baseline	79 (14) (*n* = 148)	81 (12) (*n* = 141)	–1 (–3 to 2)	0.67
	3 months	80 (15) (*n* = 134)	80 (15) (*n* = 128)		
	6 months	81 (13) (*n* = 122)	80 (14) (*n* = 112)		
	12 months	78 (15) (*n* = 107)	81 (14) (*n* = 96)		
	24 months	80 (14) (*n* = 76)	81 (13) (*n* = 75)		
KDQOL: burden of disease	Baseline	75 (25) (*n* = 148)	75 (25) (*n* = 140)	–3 (–8 to 2)	0.20
	3 months	72 (27) (*n* = 133)	77 (23) (*n* = 127)		
	6 months	74 (27) (*n* = 121)	76 (23) (*n* = 112)		
	12 months	72 (27) (*n* = 107)	75 (24) (*n* = 97)		
	24 months	72 (26) (*n* = 74)	71 (27) (*n* = 74)		
KDQOL: effect of disease	Baseline	86 (14) (*n* = 146)	87 (15) (*n* = 141)	–2 (–5 to 1)	0.25
	3 months	84 (17) (*n* = 133)	86 (16) (*n* = 127)		
	6 months	85 (15) (*n* = 122)	86 (15) (*n* = 113)		
	12 months	83 (18) (*n* = 106)	86 (16) (*n* = 97)		
	24 months	84 (16) (*n* = 74)	85 (19) (*n* = 74)		
SF-36 PCS	Baseline	36 (11) (*n* = 137)	36 (11) (*n* = 133)	–1 (–4 to 1)	0.23
	3 months	34 (11) (*n* = 127)	37 (11) (*n* = 115)		
	6 months	35 (11) (*n* = 115)	37 (11) (*n* = 106)		
	12 months	35 (12) (*n* = 102)	37 (10) (*n* = 87)		
	24 months	34 (11) (*n* = 70)	36 (12) (*n* = 69)		
SF-36 MCS	Baseline	53 (11) (*n* = 137)	54 (9) (*n* = 133)	–2 (–4 to 0)	0.03
	3 months	52 (10) (*n* = 127)	54 (9) (*n* = 115)		
	6 months	52 (10) (*n* = 115)	54 (10) (*n* = 106)		
	12 months	51 (10) (*n* = 102)	53 (10) (*n* = 87)		
	24 months	51 (10) (*n* = 70)	54 (11) (*n* = 69)		

MCS, mental component score; PCS, physical component score; SD, standard deviation.
Repeated-measures analysis of variance adjusted for baseline values, age, sex and CKD category.

TABLE 7 Secondary outcomes: measures of renal function and associated biochemistry

Outcome	Time point	Randomised group		Treatment effect[a] (95% CI)	*p*-value
		Bicarbonate	Placebo		
Bicarbonate (mmol/l), mean concentration (SD)	Baseline	20.6 (2.6) (*n* = 152)	20.1 (2.5) (*n* = 148)	1.1 (0.6 to 1.6)	< 0.001
	3 months	22.4 (2.7) (*n* = 137)	20.7 (3.4) (*n* = 133)		
	6 months	22.3 (2.7) (*n* = 124)	21.1 (3.2) (*n* = 116)		
	12 months	22.5 (2.6) (*n* = 107)	21.4 (3.9) (*n* = 98)		
	24 months	22.9 (4.1) (*n* = 79)	22.5 (3.3) (*n* = 77)		
eGFR (ml/minute/1.73 m^2), mean concentration (SD)	Baseline	19.7 (6.5) (*n* = 152)	18.2 (6.4) (*n* = 148)	0.6[b] (–0.8 to 2.0)	0.39
	3 months	18.8 (6.4) (*n* = 137)	18.7 (7.6) (*n* = 133)		
	6 months	19.0 (7.3) (*n* = 126)	18.6 (8.0) (*n* = 117)		
	12 months	17.9 (7.6) (*n* = 112)	18.1 (7.7) (*n* = 101)		
	24 months	19.5 (10.2) (*n* = 79)	18.0 (8.2) (*n* = 78)		
Creatinine (µmol/l), mean concentration (SD)	Baseline	289 (101) (*n* = 152)	307 (103) (*n* = 148)	–8[b] (–28 to 13)	0.46
	3 months	305 (118) (*n* = 137)	309 (116) (*n* = 133)		
	6 months	311 (138) (*n* = 126)	313 (120) (*n* = 117)		
	12 months	341 (177) (*n* = 112)	320 (140) (*n* = 101)		
	24 months	319 (150) (*n* = 79)	332 (150) (*n* = 78)		
Cystatin C (mg/l), mean concentration (SD)	Baseline	3.11 (0.74) (*n* = 143)	3.14 (0.74) (*n* = 136)	–0.01[b] (–0.17 to 0.14)	0.89
	3 months	3.20 (0.88) (*n* = 129)	3.21 (0.85) (*n* = 120)		
	6 months	3.21 (0.87) (*n* = 121)	3.21 (0.96) (*n* = 107)		
	12 months	3.41 (1.09) (*n* = 103)	3.33 (1.04) (*n* = 93)		
	24 months	3.39 (1.20) (*n* = 71)	3.35 (1.03) (*n* = 72)		
Urinary albumin-to-creatinine ratio, median (IQR)	Baseline	23 (7–79) (*n* = 142)	22 (7–100) (*n* = 135)	0.32[c] (–0.05 to 0.70)	0.09
	3 months	32 (8–112) (*n* = 131)	26 (5–99) (*n* = 127)		
	6 months	25 (7–106) (*n* = 113)	19 (7–76) (*n* = 110)		
	12 months	25 (7–115) (*n* = 102)	21 (8–71) (*n* = 90)		
	24 months	19 (6–91) (*n* = 63)	21 (5–53) (*n* = 69)		

IQR, interquartile range.
a Repeated-measures analysis of variance adjusted for baseline values, age, sex and CKD category.
b Repeated-measures analysis of variance adjusted for baseline values, age and sex.
c Repeated-measures analysis of variance: log-transformed value.

No difference was seen in the time to meeting criteria for a composite end point of decline in renal function, defined as a doubling of the baseline creatinine concentration, a 40% reduction in eGFR from baseline or commencement of renal replacement therapy. The hazard ratio (HR) by Cox proportional hazards modelling for reaching this composite end point, adjusted for age, sex and CKD category at baseline, was 1.03 (95% CI 0.66 to 1.63; $p = 0.88$).

Vascular health

No significant treatment effect was found for blood pressure, total cholesterol or N-terminal pro-B-type natriuretic peptide on repeated-measures analysis. The results are presented in *Table 8* and the change in blood pressure relative to baseline in each group is shown in *Figure 6*.

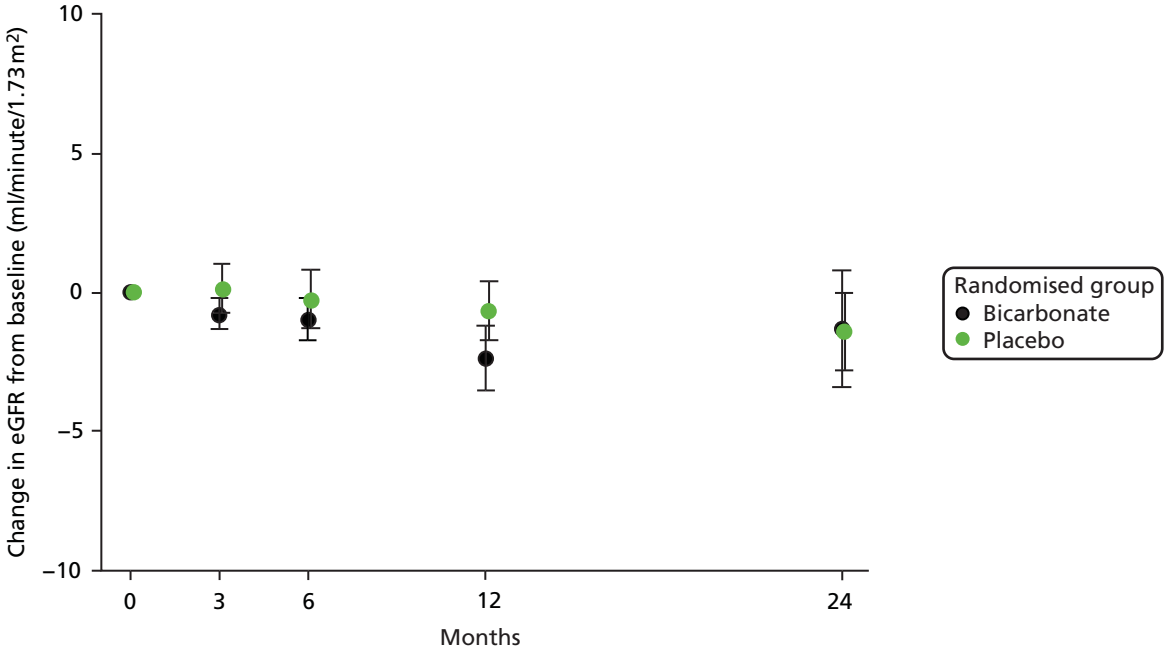

FIGURE 5 Change in eGFR relative to baseline.

TABLE 8 Secondary outcomes: markers of vascular health

Outcome	Time point	Randomised group		Treatment effect[a] (95% CI)	*p*-value
		Bicarbonate	Placebo		
NT-pro-BNP (pg/ml), median concentration (IQR)	Baseline	5910 (1678–10,221) (*n* = 115)	4453 (1555–10,521) (*n* = 115)	0.13 (–0.18 to 0.44)[b]	0.42
	12 months	6809 (1651–12,691) (*n* = 91)	4158 (1725–9743) (*n* = 79)		
	24 months	5062 (1748–10,357) (*n* = 80)	5653 (2369–13,287) (*n* = 72)		
Total cholesterol (mmol/l), mean (SD)	Baseline	4.3 (1.0) (*n* = 144)	4.2 (1.1) (*n* = 141)	0.1 (–0.2 to 0.3)	0.58
	3 months	4.4 (1.1) (*n* = 135)	4.2 (1.1) (*n* = 125)		
	6 months	4.4 (1.1) (*n* = 124)	4.2 (1.1) (*n* = 113)		
	12 months	4.4 (1.2) (*n* = 104)	4.3 (1.2) (*n* = 96)		
	24 months	4.4 (1.1) (*n* = 72)	4.4 (1.2) (*n* = 77)		
Systolic blood pressure (mmHg), mean (SD)	Baseline	143 (18) (*n* = 152)	143 (18) (*n* = 148)	0 (–4 to 3)	0.93
	3 months	143 (20) (*n* = 138)	143 (19) (*n* = 133)		
	6 months	140 (20) (*n* = 128)	141 (16) (*n* = 117)		
	12 months	143 (21) (*n* = 114)	143 (16) (*n* = 103)		
	24 months	143 (21) (*n* = 81)	142 (18) (*n* = 79)		
Diastolic blood pressure (mmHg), mean (SD)	Baseline	75 (11) (*n* = 152)	73 (10) (*n* = 148)	1 (–1 to 3)	0.16
	3 months	75 (10) (*n* = 138)	73 (11) (*n* = 133)		
	6 months	74 (12) (*n* = 128)	73 (11) (*n* = 117)		
	12 months	74 (11) (*n* = 114)	73 (9) (*n* = 103)		
	24 months	76 (11) (*n* = 81)	72 (10) (*n* = 79)		

IQR, interquartile range; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.
a Repeated-measures analysis of variance adjusted for baseline values, minimisation variables, age, sex and CKD category.
b Repeated-measures analysis of variance: log-transformed value.

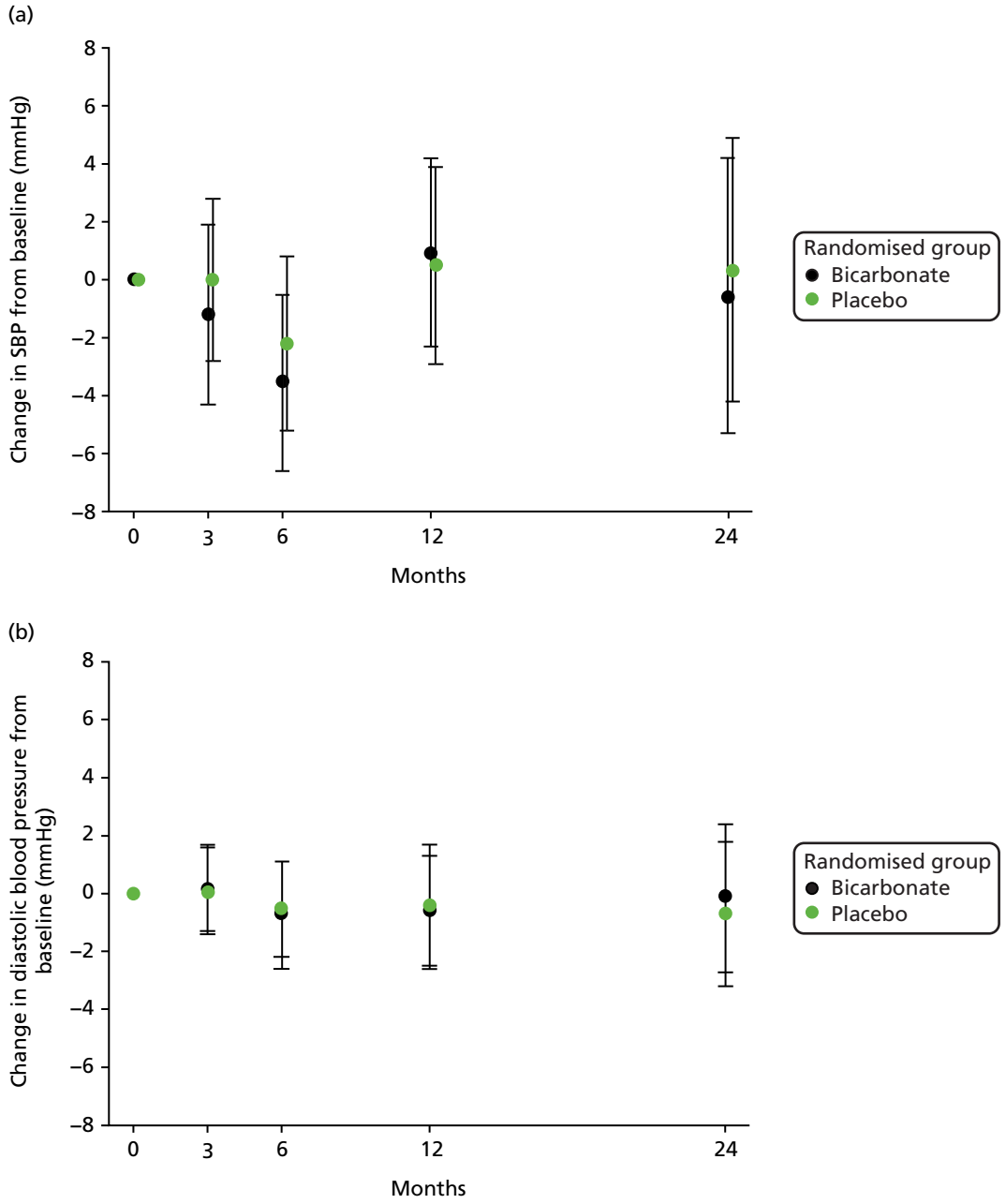

FIGURE 6 Change in blood pressure relative to baseline. (a) Change in systolic blood pressure (SBP); and (b) change in diastolic blood pressure.

Bone and mineral metabolism

No significant treatment effect was evident for markers of bone turnover (bone-specific alkaline phosphatase and tartrate-resistant acid phosphatase 5b) or for other key molecules involved in bone and mineral metabolism (vitamin D metabolites, PTH, calcium or phosphate). The results are presented in *Table 9*.

Other blood markers

No significant treatment effect was evident for blood haemoglobin and glycosylated haemoglobin (HbA_{1c}) level, thyroid function or serum albumin concentration. Of particular note, no treatment effect was evident for serum potassium concentration. The results are presented in *Table 10*.

TABLE 9 Secondary outcomes: markers of bone and mineral metabolism

Outcome	Time point	Randomised group		Treatment effect[a] (95% CI)	*p*-value
		Bicarbonate	Placebo		
TRACP-5b (IU/l), median concentration (IQR)	Baseline	0.58 (0.29–1.30) (*n* = 122)	0.88 (0.36–1.57) (*n* = 126)	–0.18 (–0.43 to 0.08)[b]	0.17
	12 months	0.72 (0.32–1.16) (*n* = 87)	0.84 (0.34–1.36) (*n* = 75)		
	24 months	0.46 (0.22–0.85) (*n* = 50)	0.58 (0.28–1.40) (*n* = 56)		
Bs-ALP (µg/l), median concentration (IQR)	Baseline	14.4 (11.5–19.7) (*n* = 124)	14.8 (11.4–19.1) (*n* = 125)	0.01 (–0.11 to 0.13)[b]	0.83
	12 months	13.6 (10.0–18.1) (*n* = 89)	13.9 (11.5–17.4) (*n* = 77)		
	24 months	13.7 (10.2–19.7) (*n* = 55)	12.6 (10.3–17.5) (*n* = 57)		
PTH (pmol/l), median concentration (IQR)	Baseline	16.5 (9.8–26.5) (*n* = 103)	15.0 (9.8–23.4) (*n* = 105)	0.03 (–0.14 to 0.19)[b]	0.75
	12 months	17.0 (9.8–30.8) (*n* = 82)	15.5 (10.2–22.0) (*n* = 81)		
	24 months	14.8 (9.6–31.5) (*n* = 58)	17.4 (12.2–24.9) (*n* = 67)		
25OHD (nmol/l), median concentration (IQR)	Baseline	33 (24–56) (*n* = 109)	41 (24–67) (*n* = 108)	–0.08 (–0.23 to 0.06)[b]	0.24
	12 months	35 (22–56) (*n* = 88)	43 (24–59) (*n* = 77)		
	24 months	42 (23–66) (*n* = 53)	48 (26–70) (*n* = 56)		
1,25OHD (pmol/l), mean concentration (SD)	Baseline	57 (23) (*n* = 109)	54 (24) (*n* = 109)	3 (–3 to 9)	0.30
	12 months	61 (40) (*n* = 88)	55 (23) (*n* = 78)		
	24 months	62 (29) (*n* = 53)	58 (28) (*n* = 56)		
Calcium (mmol/l), mean concentration (SD)	Baseline	2.33 (0.13) (*n* = 144)	2.32 (0.14) (*n* = 145)	0.02 (0.00 to 0.04)	0.11
	3 months	2.34 (0.13) (*n* = 134)	2.34 (0.14) (*n* = 129)		
	6 months	2.34 (0.11) (*n* = 123)	2.34 (0.15) (*n* = 115)		
	12 months	2.35 (0.11) (*n* = 107)	2.33 (0.12) (*n* = 100)		
	24 months	2.37 (0.11) (*n* = 78)	2.34 (0.11) (*n* = 76)		
Phosphate (mmol/l), mean concentration (SD)	Baseline	1.26 (0.39) (*n* = 142)	1.29 (0.27) (*n* = 140)	0.02 (–0.03 to 0.06)	0.52
	3 months	1.26 (0.26) (*n* = 123)	1.28 (0.31) (*n* = 123)		
	6 months	1.26 (0.26) (*n* = 115)	1.23 (0.27) (*n* = 106)		
	12 months	1.27 (0.30) (*n* = 106)	1.28 (0.36) (*n* = 97)		
	24 months	1.25 (0.27) (*n* = 75)	1.24 (0.34) (*n* = 77)		

1,25OHD, 1,25-dihydroxyvitamin D; 25OHD, 25-hydroxyvitamin D; Bs-ALP, bone-specific alkaline phosphatase; IQR, interquartile range; TRACP-5b, tartrate-resistant acid phosphatase 5b.

a Repeated-measures analysis of variance adjusted for baseline values, minimisation variables, age, sex and CKD category.

b Repeated-measures analysis of variance: log-transformed values.

TABLE 10 Secondary analyses: other blood markers

Outcome	Time point	Randomised group		Treatment effect[a] (95% CI)	*p*-value
		Bicarbonate	Placebo		
Haemoglobin, mean concentration (SD) (g/l)	Baseline	115 (14) (*n* = 142)	117 (17) (*n* = 144)	–0.1 (–0.4 to 0.2)	0.48
	3 months	117 (15) (*n* = 138)	119 (15) (*n* = 131)		
	6 months	118 (13) (*n* = 126)	118 (16) (*n* = 117)		
	12 months	116 (15) (*n* = 112)	120 (15) (*n* = 101)		
	24 months	120 (14) (*n* = 77)	120 (16) (*n* = 78)		
Albumin (g/l), mean concentration (SD)	Baseline	39 (4) (*n* = 148)	40 (5) (*n* = 146)	0 (–1 to 1)	0.67
	3 months	39 (5) (*n* = 135)	39 (5) (*n* = 132)		
	6 months	39 (5) (*n* = 124)	39 (5) (*n* = 116)		
	12 months	39 (5) (*n* = 109)	39 (5) (*n* = 100)		
	24 months	39 (5) (*n* = 79)	39 (4) (*n* = 78)		
Median concentration of TSH (IQR)	Baseline	2.1 (1.5–3.0) (*n* = 138)	2.1 (1.5–2.8) (*n* = 137)	0.07 (–0.10 to 0.24)[b]	0.39
	3 months	2.2 (1.4–3.1) (*n* = 129)	1.9 (1.3–2.8) (*n* = 124)		
	6 months	2.1 (1.4–3.3) (*n* = 120)	2.2 (1.4–3.3) (*n* = 109)		
	12 months	2.2 (1.3–3.6) (*n* = 100)	2.1 (1.5–2.9) (*n* = 93)		
	24 months	2.5 (1.4–3.1) (*n* = 74)	2.2 (1.2–3.1) (*n* = 75)		
Potassium (mmol/l), mean concentration (SD)	Baseline	4.9 (0.5) (*n* = 149)	4.9 (0.5) (*n* = 148)	0.0 (–0.1 to 0.1)	0.80
	3 months	4.8 (0.5) (*n* = 136)	4.9 (0.6) (*n* = 130)		
	6 months	4.9 (0.5) (*n* = 124)	4.8 (0.5) (*n* = 116)		
	12 months	4.8 (0.5) (*n* = 112)	4.8 (0.5) (*n* = 101)		
	24 months	4.8 (0.6) (*n* = 77)	4.8 (0.5) (*n* = 78)		
HbA_{1c} (mmol/mol), mean concentration (SD)	Baseline	43 (12) (*n* = 134)	42 (13) (*n* = 131)	1 (–1 to 4)	0.38
	3 months	44 (15) (*n* = 131)	42 (12) (*n* = 126)		
	6 months	45 (15) (*n* = 124)	43 (13) (*n* = 115)		
	12 months	44 (14) (*n* = 103)	42 (11) (*n* = 92)		
	24 months	42 (11) (*n* = 67)	43 (11) (*n* = 68)		

TSH, thyroid-stimulating hormone.
a Repeated-measures analysis of variance: adjusted for baseline values, minimisation variables, age, sex and CKD category.
b Repeated-measures analysis of variance: log-transformed values.

Adverse events

A large number of adverse events (*n* = 857) were recorded, as expected for a trial enrolling older patients with extensive multimorbidity. In total, 263 out of 300 (88%) participants experienced at least one adverse event. Adverse events were more frequent in the bicarbonate arm (457 vs. 400), with a notable excess of events coded as gastrointestinal (45 vs. 25), musculoskeletal (28 vs. 17), cardiac (32 vs. 19), nervous system (24 vs. 12) and respiratory (26 vs. 14). Full details are presented in *Table 11*.

TABLE 11 Adverse events by System Order Class

Adverse event	Randomised group	
	Bicarbonate (*N* = 152)	Placebo (*N* = 148)
At least one adverse event, *n* (%)	131 (86.1)	132 (89.1)
Number of adverse events	457	400
SOC classification, number of events		
Blood and lymphatic system disorders	5	1
Cardiac disorders	32	19
Congenital, familial and genetic disorders	0	1
Ear and labyrinth disorders	1	1
Endocrine disorders	1	2
Eye disorders	6	6
Gastrointestinal disorders	45	25
General disorders and administration site conditions	14	20
Hepatobiliary disorders	0	0
Immune system disorders	0	0
Infections and infestations	113	118
Injury, poisoning and procedural complications	41	32
Investigations	5	7
Metabolism and nutrition disorders	19	27
Musculoskeletal and connective tissue disorders	28	17
Neoplasms – benign, malignant and unspecified (incl. cysts and polyps)	9	16
Nervous system disorders	24	12
Psychiatric disorders	1	5
Renal and urinary disorders	23	23
Reproductive system and breast disorders	4	1
Respiratory, thoracic and mediastinal disorders	26	14
Skin and subcutaneous tissue disorders	16	11
Surgical and medical procedures	34	30
Vascular disorders	10	12

SOC, System Order Class.

For cardiac adverse events, no difference in the number of episodes of decompensated heart failure was seen (8 vs. 10), but myocardial infarction was more common in the bicarbonate arm (10 vs. 2) (*Table 12*).

Need for renal replacement therapy

In total, 66 out of 300 (22%) participants commenced dialysis or underwent renal transplantation during the trial, with no difference between the bicarbonate arm and the placebo arm (33 vs. 33; $p = 1.0$) (see *Table 12*). Time-to-event analysis showed no significant difference in the HR between groups (HR 1.22, 95% CI 0.74 to 2.02; $p = 0.43$) (*Figure 7*). Similar results were seen for time to a composite outcome of either doubling of serum creatinine concentration or commencement of renal replacement therapy (HR 1.16, 95% CI 0.73 to 1.84; $p = 0.53$).

TABLE 12 Selected key adverse events of interest

Adverse event	Randomised group	
	Bicarbonate ($N = 152$)	Placebo ($N = 148$)
Deaths (all), *n* (%)	15 (9.9)	11 (7.4)
Death from cardiovascular event, *n* (%)	4 (2.6)	5 (3.4)
Death from end-stage renal failure, *n* (%)	3 (2.0)	0 (0)
Commenced dialysis or transplanted, *n* (%)	33 (21.7)	33 (22.3)
Myocardial infarction or acute coronary syndrome, *n* (%)	10 (6.6)	2 (1.4)
Decompensated heart failure or pulmonary oedema, *n* (%)	8 (5.3)	10 (6.8)
Fragility fractures (distal radius, vertebra or neck of femur), *n* (%)	5 (3.3)	2 (1.4)
At least one fall, *n* (%)	49 (32.2)	39 (26.4)
Number of falls	124	70
Falls rate (per year) (95% CI)	0.99 (0.61 to 1.38)	0.72 (0.25 to 1.19)

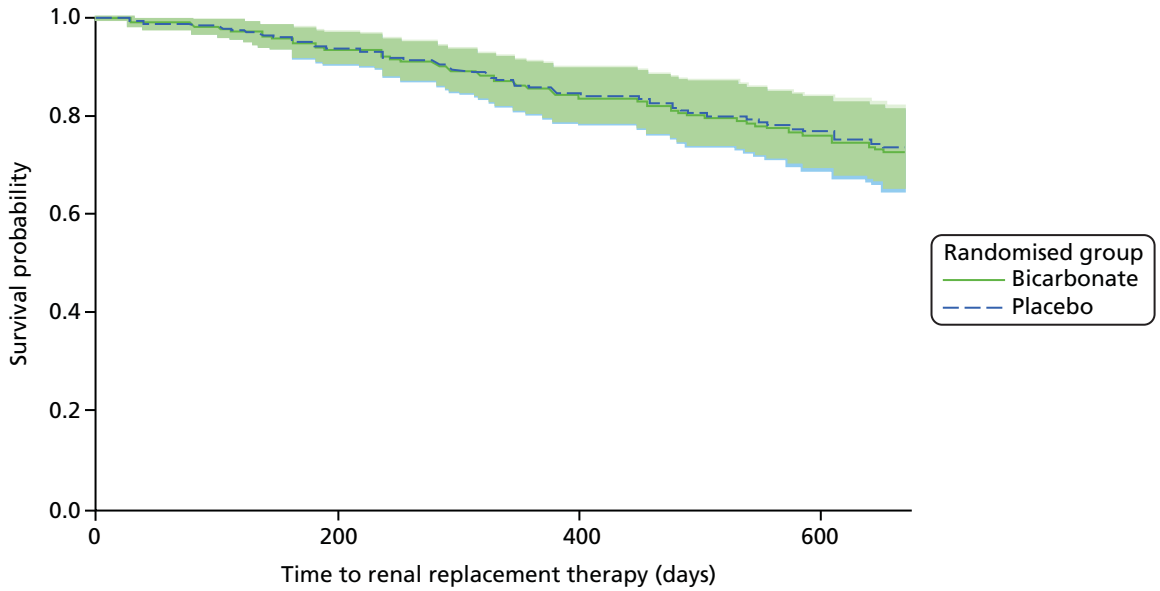

FIGURE 7 Time to commencement of renal replacement therapy. HR (adjusted for age, sex and CKD category): 1.22 (95% CI 0.74 to 2.02; $p = 0.43$).

Deaths

Twenty-six deaths were recorded during the trial, with a similar number of deaths in each arm (bicarbonate vs. placebo: 15 vs. 11; $p = 0.45$) (see *Table 12*). Time-to-event analysis showed no significant difference in HR between groups (HR 1.30, 95% CI 0.60 to 2.83; $p = 0.51$) (*Figure 8*).

Falls

More participants in the bicarbonate arm than in the placebo arm reported falling but this did not reach significance (bicarbonate vs. placebo: 49 vs. 39; $p = 0.26$). The median time to first fall among those who fell was shorter in the bicarbonate arm (130 days vs. 194 days). Cox proportional hazards modelling of time to first fall, adjusted for age, sex and CKD category, gave a HR of 1.43 (95% CI 0.94 to 2.20; $p = 0.09$).

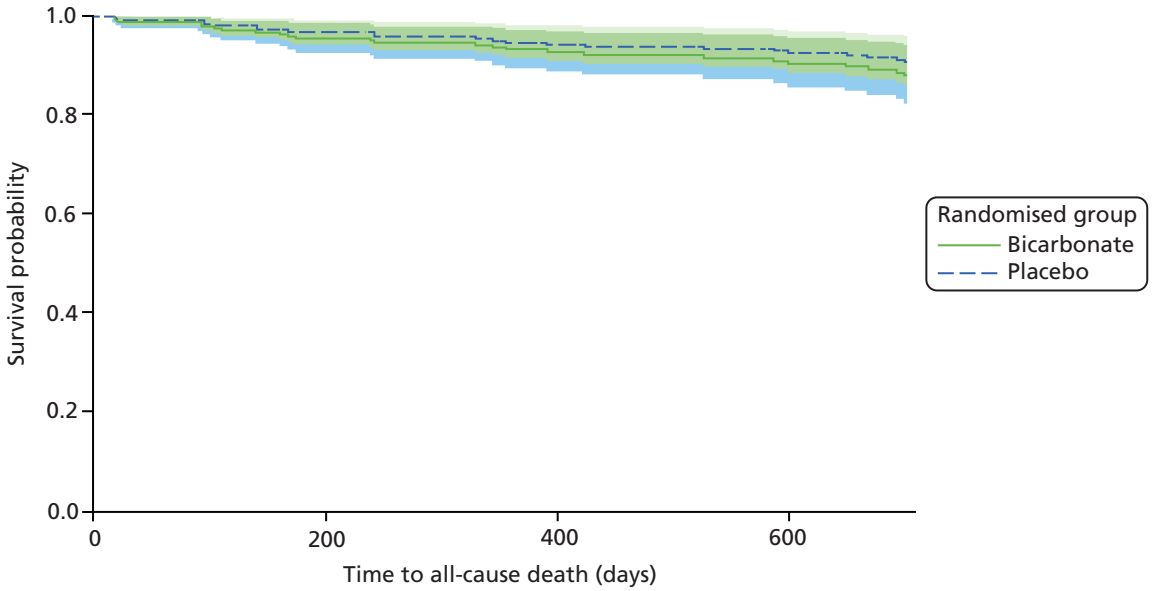

FIGURE 8 Time to death. HR (adjusted for age, sex and CKD category): 1.30 (95% CI 0.60 to 2.83; $p = 0.51$).

Meta-analysis of outcomes with the BiCARB trial data included

Figures 9–15 show the results of the meta-analyses of existing trials of bicarbonate therapy, but with the BiCARB trial results added. The increase in serum bicarbonate seen with treatment in the BiCARB trial was lower than that seen in most other trials, and the favourable effect on eGFR seen in other trials was also not seen in the BiCARB trial. Meta-analyses including BiCARB data showed no significant effect of bicarbonate treatment on weight, mid-arm muscle circumference or systolic blood pressure. Heterogeneity was high across all analyses, as shown by the high I^2 values.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
Mathur *et al.*[22]	22.93	7.12	20	17.89	4.67	20	6.8	5.04 (1.31 to 8.77)	2006
de Brito-Ashurst *et al.*[23]	25	3	62	20	3	67	13.1	5.00 (3.96 to 6.04)	2009
Mahajan *et al.*[24]	26.4	0.6	37	26.1	0.8	34	14.0	0.30 (–0.03 to 0.63)	2010
Goraya *et al.*[25]	24	0.6	36	22.4	0.6	36	14.1	1.60 (1.32 to 1.88)	2014
Jeong *et al.*[26]	1.28	3.56	37	–2.42	3.82	36	11.6	3.70 (2.01 to 5.39)	2014
Bellasi *et al.*[27]	26	2	71	22.3	1.9	74	13.7	3.70 (3.06 to 4.34)	2016
Dubey *et al.*[28]	23.5	2.7	88	17.8	2.5	89	13.5	5.70 (4.93 to 6.47)	2018
BiCARB	2.1	3.2	105	1.1	3.8	97	13.2	1.00 (0.03 to 1.97)	2019
Total (95% CI)			456			453	100.0	3.10 (1.75 to 4.46)	

Heterogeneity: $\tau^2 = 3.38$; $\chi^2 = 260.98$, df = 7 ($p < 0.00001$); $I^2 = 97\%$

Test for overall effect: $z = 4.49$ ($p < 0.00001$)

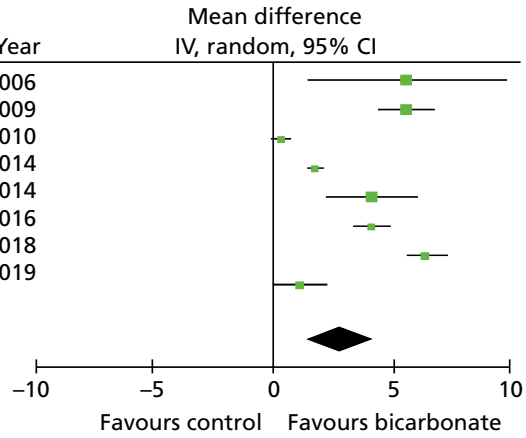

FIGURE 9 Meta-analysis: difference in serum bicarbonate concentration (mmol/l) (any time point). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
de Brito-Ashurst *et al.*[23]	23	4	62	20	3	67	24.5	3.00 (1.77 to 4.23)	2009
Jeong *et al.*[26]	1.3	3.6	37	–2.4	3.8	36	20.9	3.70 (2.00 to 5.40)	2014
Bellasi *et al.*[27]	26	2	71	22.3	1.9	74	28.3	3.70 (3.06 to 4.34)	2016
BiCARB	2.1	3.2	105	1.1	3.8	97	26.3	1.00 (0.03 to 1.97)	2019
Total (95% CI)			275			274	100.0	2.82 (1.41 to 4.22)	

Heterogeneity: $\tau^2 = 1.71$; $\chi^2 = 21.53$, df = 3 ($p < 0.0001$); $I^2 = 86\%$

Test for overall effect: $z = 3.93$ ($p < 0.0001$)

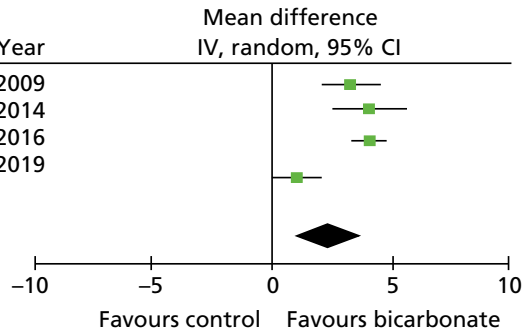

FIGURE 10 Meta-analysis: difference in serum bicarbonate concentration (mmol/l) (1-year follow-up only). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
de Brito-Ashurst *et al.*[23]	20	5	62	17	5	67	16.0	3.00 (1.27 to 4.73)	2009
Mahajan *et al.*[24]	67.6	4.9	37	64	6.1	34	13.8	3.60 (1.01 to 6.19)	2010
Goraya *et al.*[25]	35.2	6.9	36	28.8	7.3	36	12.0	6.40 (3.12 to 9.68)	2014
Jeong *et al.*[26]	–2.1	2.1	37	–3.2	2	36	17.6	1.10 (0.16 to 2.04)	2014
Bellasi *et al.*[27]	32	15	71	31	16	74	8.2	1.00 (–4.05 to 6.05)	2016
Dubey *et al.*[28]	32.7	5.9	88	28.2	5.9	89	16.0	4.50 (2.76 to 6.24)	2018
BiCARB	–2.4	6.1	111	–0.6	5.5	100	16.4	–1.80 (–3.37 to –0.23)	2019
Total (95% CI)			442			436	100.0	2.45 (0.51 to 4.39)	

Heterogeneity: $\tau^2 = 5.33$; $\chi^2 = 42.94$, df = 6 ($p < 0.00001$); $I^2 = 86\%$

Test for overall effect: $z = 2.47$ ($p = 0.01$)

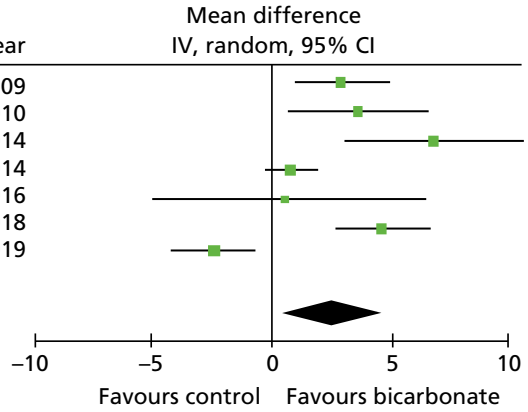

FIGURE 11 Meta-analysis: difference in eGFR (ml/minute/1.73 m²) (any time point). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
de Brito-Ashurst *et al.*[23]	20	6	62	20	6	67	27.8	0.00 (–2.07 to 2.07)	2009
Jeong *et al.*[26]	–2	3.4	37	–4.8	5.2	36	28.1	2.80 (0.78 to 4.82)	2014
Bellasi *et al.*[27]	32	15	71	31	16	74	13.4	1.00 (–4.05 to 6.05)	2016
BiCARB	–2.4	6.1	111	–0.6	5.5	100	30.7	–1.80 (–3.37 to –0.23)	2019
Total (95% CI)			281			277	100.0	0.37 (–1.98 to 2.71)	

Heterogeneity: $\tau^2 = 4.03$; $\chi^2 = 12.60$, df = 3 ($p = 0.006$); $I^2 = 76\%$

Test for overall effect: $z = 0.31$ ($p = 0.76$)

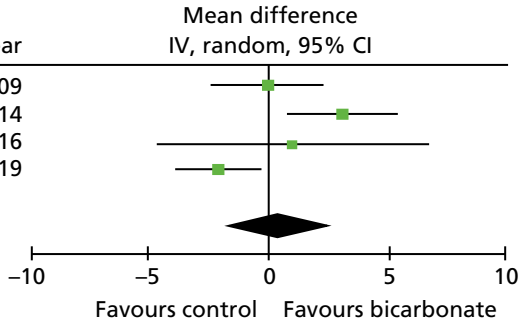

FIGURE 12 Meta-analysis: difference in eGFR (ml/minute/1.73 m²) (1-year follow-up only). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
Mathur *et al.*[22]	140	4	20	134	4	20	18.1	6.00 (3.52 to 8.48)	2006
de Brito-Ashurst *et al.*[23]	122	4	62	122	8	67	19.1	0.00 (–2.16 to 2.16)	2009
Mahajan *et al.*[24]	135.1	6.2	37	133.3	8.1	34	15.3	1.80 (–1.58 to 5.18)	2010
Goraya *et al.*[25]	135.7	4.5	36	135.4	6.2	36	18.0	0.30 (–2.20 to 2.80)	2014
Bellasi *et al.*[27]	125	17	71	121	16	74	10.1	4.00 (–1.38 to 9.38)	2016
Dubey *et al.*[28]	124	24.7	88	128	19.8	89	7.9	–4.00 (–10.60 to 2.60)	2018
BiCARB	0.9	17.4	103	0.5	17.3	103	11.5	0.40 (–4.34 to 5.14)	2019
Total (95% CI)			417			423	100.0	1.55 (–0.73 to 3.83)	

Heterogeneity: $\tau^2 = 5.87$; $\chi^2 = 19.00$, df = 6 ($p = 0.004$); $I^2 = 68\%$

Test for overall effect: $z = 1.33$ ($p = 0.18$)

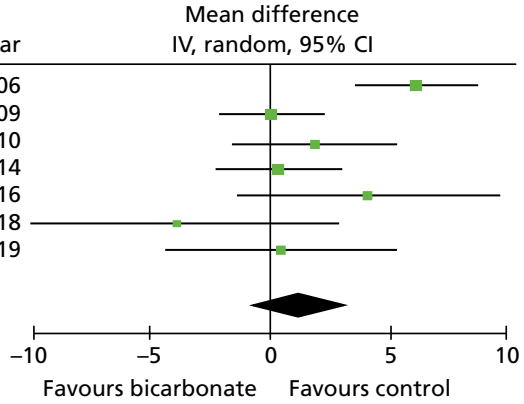

FIGURE 13 Meta-analysis: difference in systolic blood pressure (mmHg) (any time point). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
Mathur *et al.*[22]	58.4	1.2	20	59.4	0.9	20	24.1	–1.00 (–1.66 to –0.34)	2006
Goraya *et al.*[25]	83.9	5.9	36	81.2	6	36	8.9	2.70 (–0.05 to 5.45)	2014
Jeong *et al.*[26]	0.64	2.6	37	–0.12	2.59	36	19.5	0.76 (–0.43 to 1.95)	2014
Bellasi *et al.*[27]	76.3	12.8	71	73.4	15	74	4.1	2.90 (–1.63 to 7.43)	2016
Dubey *et al.*[28]	54.1	0.35	88	53.3	0.3	89	26.8	0.80 (0.70 to 0.90)	2018
BiCARB	–0.3	5.1	112	–0.5	6.2	102	16.5	0.20 (–1.33 to 1.73)	2019
Total (95% CI)			364			357	100.0	0.52 (–0.49 to 1.52)	

Heterogeneity: $\tau^2 = 0.97$; $\chi^2 = 31.48$, df = 5 ($p < 0.00001$); $I^2 = 84\%$

Test for overall effect: $z = 1.01$ ($p = 0.31$)

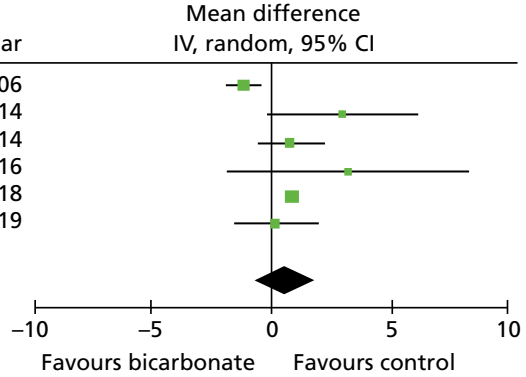

FIGURE 14 Meta-analysis: difference in weight (kg) (any time point). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
de Brito-Ashurst *et al.*[23]	26.3	0.6	62	24.5	0.5	67	27.0	1.80 (1.61 to 1.99)	2009
Jeong *et al.*[26]	0.28	2.37	37	0.31	1.74	36	22.6	–0.03 (–0.98 to 0.92)	2014
Dubey *et al.*[28]	22.8	0.05	88	22.6	0.05	89	27.2	0.20 (0.19 to 0.21)	2018
BiCARB	–0.4	2.6	107	–0.7	3.7	99	23.2	0.30 (–0.58 to 1.18)	2019
Total (95% CI)			294			291	100.0	0.60 (–0.50 to 1.71)	

Heterogeneity: $\tau^2 = 1.16$; $\chi^2 = 267.11$, df = 3 ($p < 0.00001$); $I^2 = 99\%$

Test for overall effect: $z = 1.07$ ($p = 0.28$)

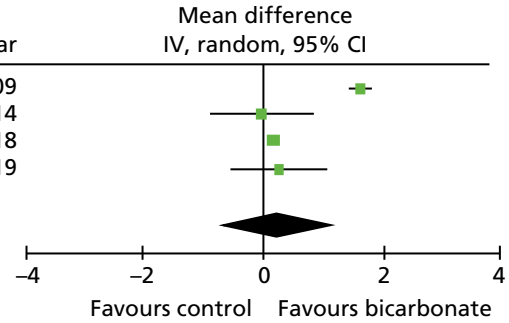

FIGURE 15 Meta-analysis: difference in mid-arm muscle circumference (cm) (any time point). IV, instrumental variable; SD, standard deviation.

Chapter 5 Cost-effectiveness results

Table 13 shows the main resource use and costs per participant for complete cases over the first 12 months of follow-up. These initial analyses do not take into account participants who dropped out at the point of commencing renal replacement therapy, which is considered later in this chapter. All cost-effectiveness analyses are based on the unit costs reported in *Appendix 4*. The most frequently used resource use item was GP visits (63–64% of study participants). The next most frequently used item was outpatient visits (from 60% to 62% for nephrology visits and between 57% and 62% for other outpatient visits). The most expensive resource use item was an inpatient hospital stay, with a mean cost of £480 (bicarbonate arm) or £175 (placebo arm). The least frequently used items were physiotherapy, occupational therapy, speech therapy and social care. Totalling all resource use together over 1 year, costs were lowest among participants randomised to the placebo arm (mean cost £807 per participant in the placebo arm vs. £1234 per participant in the bicarbonate arm).

TABLE 13 Mean resource use and costs per participant over 12 months' follow-up (complete-case analysis, $n = 176$)

	Randomised group					
	Bicarbonate ($N = 97$)			Placebo ($N = 79$)		
Resource use item	Resource users, *n* (%)	Mean (SD) resource use	Mean (SD) cost (£)	Resource users, *n* (%)	Mean (SD) resource use	Mean (SD) cost (£)
NHS hospital care						
Admission days	8 (8)	1.39 (6.24)	480.41 (2152.51)	9 (11)	0.51 (1.66)	174.77 (571.41)
Day cases	16 (16)	0.24 (0.69)	182.01 (509.55)	7 (9)	0.11 (0.39)	83.80 (288.23)
Outpatient visits: nephrology	58 (60)	1.06 (1.09)	200.12 (333.47)	49 (62)	1.25 (1.73)	215.24 (339.65)
Outpatient visits: other	60 (62)	1.46 (1.79)	175.43 (214.70)	45 (57)	1.54 (1.89)	185.07 (226.08)
Day hospital visits	24 (25)	0.55 (1.66)	72.25 (219.30)	19 (24)	0.46 (1.47)	60.26 (194.98)
Total hospital-based care costs			1110.22 (2261.83)			719.15 (972.64)
NHS primary care						
GP visits	62 (64)	1.51 (1.64)	57.20 (62.33)	50 (63)	1.38 (1.66)	52.43 (63.03)
District nurse visits	25 (26)	1.31 (6.36)	48.35 (234.92)	23 (29)	0.62 (1.56)	22.91 (57.73)
Physiotherapist visits	7 (7)	0.15 (0.74)	8.04 (38.54)	1 (1)	0.01 (0.11)	0.66 (5.85)
Occupational therapist visits	4 (4)	0.04 (0.20)	2.97 (14.40)	1 (1)	0.01 (0.11)	0.91 (8.11)
Speech therapist visits	0 (0)	0	0	1 (1)	0.01 (0.11)	1.27 (11.32)
Social services						
Day centre visits	5 (5)	0.10 (0.51)	6.49 (32.13)	2 (3)	0.11 (0.91)	7.18 (57.06)
Home help/carer visits	1 (1)	0.06 (0.61)	0.94 (9.27)	4 (5)	0.16 (0.78)	2.50 (11.84)
Total non-hospital-based care costs			123.00 (241.42)			87.86 (103.11)
Total costs			1234.22 (2334.29)			807.01 (1005.91)

SD, standard deviation.

Table 14 describes the main resource use and costs per participant for complete cases over the first 24 months of follow-up. Owing to the additional numbers of participants dropping out over this extended follow-up period, the number of complete cases fell to 114 for this analysis. Totalling all resource use together over 2 years, costs were lowest among participants randomised to the bicarbonate group (mean cost £1184 per participant in the bicarbonate group vs. £1266 per participant in the placebo group).

The above analyses do not account for the costs of renal replacement (dialysis and renal transplantation) for participants who exited the study. Over the course of 2 years of follow-up, 66 participants proceeded to dialysis or transplantation, but 49 of these withdrew from the trial, commonly at the point of commencing renal replacement therapy. *Table 15* includes all dialysis participants as well as complete cases. Their dialysis costs are calculated by using information on the type of dialysis and the date that dialysis commenced. The remaining health-care costs are missing for these participants once they are lost to follow-up. *Table 15* shows that dialysis costs dominate other costs in both arms. Totalling all resource use together over 2 years, costs were lowest among participants in the bicarbonate group (mean cost £12,125 per participant in the bicarbonate group vs. £12,967 per participant in the placebo group).

TABLE 14 Mean resource use and costs per participant over 24 months' follow-up (complete-case analysis, $n = 114$)

	Randomised group					
	Bicarbonate ($N = 59$)			Placebo ($N = 55$)		
Resource use item	Resource users, *n* (%)	Mean (SD) resource use	Mean (SD) cost (£)	Resource users, *n* (%)	Mean (SD) resource use	Mean (SD) cost (£)
NHS hospital care						
Admission days	6 (10)	0.68 (2.58)	234.02 (891.50)	8 (15)	1.05 (4.36)	364.01 (1505.22)
Day cases	9 (15)	0.19 (0.47)	137.15 (347.58)	8 (15)	0.18 (0.47)	133.75 (349.39)
Outpatient visits: nephrology	40 (68)	1.39 (1.47)	275.45 (401.21)	35 (64)	1.56 (2.04)	306.43 (469.62)
Outpatient visits: other	41 (69)	1.93 (2.38)	231.56 (284.87)	35 (64)	1.89 (2.27)	226.61 (271.59)
Day hospital visits	21 (36)	1.08 (2.62)	143.44 (346.63)	15 (27)	0.84 (3.30)	110.59 (436.16)
Total hospital-based care costs			1021.62 (1357.52)			1141.39 (1939.44)
NHS primary care						
GP visits	49 (83)	2.07 (1.79)	78.58 (68.00)	39 (71)	1.98 (2.15)	75.31 (81.60)
District nurse visits	18 (31)	1.15 (2.88)	42.56 (106.20)	21 (38)	0.94 (2.14)	34.92 (78.96)
Physiotherapist visits	6 (10)	0.25 (0.96)	13.23 (49.81)	0 (0)	0	0
Occupational therapist visits	1 (2)	0.02 (0.13)	1.22 (9.38)	1 (2)	0.02 (0.13)	1.31 (9.72)
Speech therapist visits	0 (0)	0	0	0 (0)	0	0
Social services						
Day centre visits	4 (7)	0.39 (2.15)	24.56 (135.43)	2 (4)	0.16 (1.08)	10.31 (68.33)
Home help/carer visits	2 (3)	0.15 (0.94)	2.32 (14.35)	3 (5)	0.24 (1.00)	3.60 (15.20)
Total non-hospital-based care costs			162.47 (247.16)			125.44 (144.08)
Total costs			1184.08 (1432.11)			1266.83 (1958.68)

SD, standard deviation.

TABLE 15 Mean resource use and costs per participant over 24 months' follow-up (complete cases and all participants starting renal replacement therapy during the trial, $n = 163$)

	Randomised group					
	Bicarbonate ($N = 82$)			Placebo ($N = 81$)		
Resource use item	Resource users, *n* (%)	Mean (SD) resource use	Mean (SD) cost (£)	Resource users, *n* (%)	Mean (SD) resource use	Mean (SD) cost (£)
NHS hospital care						
Admission days	11 (13)	2.24 (8.96)	774.55 (3091.46)	12 (15)	1.74 (7.87)	600.87 (2715.09)
Day cases	14 (17)	0.20 (0.46)	143.54 (335.79)	11 (14)	0.16 (0.43)	118.06 (317.61)
Outpatient visits: nephrology	53 (65)	1.32 (1.40)	198.19 (211.33)	47 (58)	1.51 (2.25)	226.65 (338.27)
Outpatient visits: other	55 (67)	1.96 (2.39)	235.30 (286.48)	46 (57)	1.62 (2.11)	193.82 (252.50)
Dialysis visits (haemodialysis, peritoneal dialysis)	32 (39)	88.55 (136.08)	10,344.34 (14,888.34)	29 (36)	99.18 (168.53)	10,982.17 (17,254.63)
Renal transplant	1 (1)	0.01 (0.11)	154.64 (1400.35)	4 (5)	0.05 (0.22)	626.21 (2764.58)
Day hospital visits	27 (33)	0.91 (2.31)	120.94 (305.51)	22 (27)	0.80 (3.01)	106.11 (398.57)
Total hospital-based care costs			11,971.5 (15,495.88)			12,853.88 (17,430.03)
NHS primary care						
GP visits	62 (76)	1.90 (1.79)	72.29 (68.00)	51 (63)	1.78 (2.08)	67.56 (79.03)
District nurse visits	24 (29)	1.22 (2.73)	41.43 (100.74)	25 (31)	0.80 (1.94)	29.64 (71.61)
Physiotherapist visits	7 (9)	0.22 (0.88)	11.42 (45.53)	1 (1)	0.02 (0.22)	1.28 (11.56)
Occupational therapist visits	2 (2)	0.02 (0.16)	1.76 (11.18)	2 (2)	0.02 (0.16)	1.78 (11.25)
Speech therapist visits	0 (0)	0	0	0 (0)	0	0
Social service						
Day centre visits	8 (10)	0.39 (1.88)	24.59 (118.69)	2 (2)	0.11 (0.89)	7.00 (56.35)
Home help/carer visits	3 (4)	0.13 (0.83)	2.04 (12.59)	4 (5)	0.40 (2.25)	6.01 (34.24)
Total non-hospital-based care costs			153.54 (219.96)			113.33 (139.86)
Total costs			12,125.03 (15,494.49)			12,967.15 (17,430.3)

SD, standard deviation.

Tables 16 and *17* show the mean EQ-5D values and QALY over 12 and 24 months, respectively, for complete cases. The EQ-5D value was lower at baseline for the bicarbonate group for the analysis at 12 and 24 months (0.73 and 0.74, respectively) than for the placebo group (0.78 and 0.79, respectively). At 12 months' follow-up, the mean EQ-5D value had increased in the placebo group (0.79) and had decreased in the bicarbonate group (0.69). At 24 months' follow-up, the mean EQ-5D value had fallen in both groups, by approximately 0.05 in the placebo group and by 0.03 in the treatment group. Overall, the total QALYs were higher in the placebo group at both 12 and 24 months' follow-up.

TABLE 16 Mean EQ-5D values and QALYs over 12 months' follow-up by randomised group (complete-case analysis, $n = 176$)

	Randomised group, mean (SD)	
Time point	Bicarbonate ($n = 97$)	Placebo ($n = 79$)
Baseline	0.733 (0.216)	0.779 (0.219)
3 months	0.720 (0.209)	0.801 (0.152)
6 months	0.728 (0.190)	0.782 (0.167)
12 months	0.692 (0.230)	0.787 (0.151)
Total QALYs over 12 months	0.717 (0.178)	0.788 (0.145)

SD, standard deviation.

TABLE 17 Mean EQ-5D values and QALYs over 24 months' follow-up by randomised group (complete-case analysis, $n = 114$)

	Randomised group, mean (SD)	
Time point	Bicarbonate ($n = 59$)	Placebo ($n = 55$)
Baseline	0.740 (0.204)	0.786 (0.203)
3 months	0.700 (0.223)	0.808 (0.127)
6 months	0.730 (0.163)	0.802 (0.147)
12 months	0.707 (0.219)	0.794 (0.136)
24 months	0.709 (0.254)	0.731 (0.187)
Total QALYs over 24 months	1.402 (0.185)	1.537 (0.235)

SD, standard deviation.

Tables 18 and *19* describe the mean ICECAP-O values over 12 and 24 months, respectively, for complete cases. In contrast to the EQ-5D and QALY analyses, the baseline differences between the groups are smaller and, for both groups, the differences in values between baseline and follow-up are smaller relative to the EQ-5D values. *Tables 20* and *21* show the mean life satisfaction values over 12 and 24 months, respectively, for complete cases. The changes over time for both groups are consistent with the EQ-5D and ICECAP (Investigating Choice Experiments for the preferences of older people CAPability) data.

TABLE 18 Mean ICECAP-O values over 12 months' follow-up by randomised group (complete-case analysis, $n = 176$)

	Randomised group, mean (SD)	
Time point	Bicarbonate ($n = 97$)	Placebo ($n = 79$)
Baseline	0.861 (0.118)	0.875 (0.103)
3 months	0.867 (0.108)	0.872 (0.110)
6 months	0.861 (0.125)	0.885 (0.092)
12 months	0.846 (0.124)	0.892 (0.092)

SD, standard deviation.

TABLE 19 Mean ICECAP-O values over 24 months' follow-up by randomised group (complete-case analysis, $n = 114$)

	Randomised group, mean (SD)	
Time point	Bicarbonate ($n = 59$)	Placebo ($n = 55$)
Baseline	0.871 (0.105)	0.880 (0.098)
3 months	0.869 (0.102)	0.870 (0.110)
6 months	0.868 (0.127)	0.897 (0.080)
12 months	0.848 (0.120)	0.893 (0.088)
24 months	0.857 (0.110)	0.873 (0.104)

SD, standard deviation.

TABLE 20 Mean life satisfaction values over 12 months' follow-up by randomised group (complete-case analysis, $n = 176$)

	Randomised group, mean (SD)	
Time point	Bicarbonate ($n = 97$)	Placebo ($n = 79$)
Baseline	5.206 (1.607)	5.329 (1.677)
3 months	5.226 (1.623)	5.405 (1.660)
6 months	5.000 (1.683)	5.329 (1.708)
12 months	4.856 (1.633)	5.443 (1.534)

SD, standard deviation.

TABLE 21 Mean life satisfaction values over 24 months' follow-up by randomised group (complete-case analysis, $n = 114$)

	Randomised group, mean (SD)	
Time point	Bicarbonate ($n = 59$)	Placebo ($n = 55$)
Baseline	5.203 (1.517)	5.273 (1.683)
3 months	5.186 (1.559)	5.582 (1.572)
6 months	5.000 (1.462)	5.364 (1.747)
12 months	4.763 (1.568)	5.491 (1.477)
24 months	4.949 (1.569)	5.055 (1.840)

SD, standard deviation.

Table 22 shows the adjusted incremental costs and QALYs (ICECAP-O and life satisfaction values in sensitivity analyses) for the bicarbonate group versus the placebo group for the complete-case analyses at 12 and 24 months and for the complete cases plus imputed renal replacement therapy cases at 24 months. The 12- and 24-month analyses show a statistically significant increase in costs associated with bicarbonate treatment (between £564 and £591 per participant). The addition of the renal replacement therapy participants and their associated costs leads to a higher, but non-significant, cost difference (£809 per participant). In all three analyses, there is a QALY difference in favour of the placebo group (ranging from 0.05 to 0.08 QALYs).

TABLE 22 Adjusted[a] mean incremental costs, incremental QALYs and incremental cost-effectiveness ratio for sodium bicarbonate vs. placebo

Analysis	Incremental mean costs (95% CI) (£)[b,c,d]	Incremental mean QALYs (95% CI)[b,c,d]	ICER (£/QALY)
Complete cases over 12 months' follow-up ($n = 176$)[e]	563.74 (88.18 to 1154.18)	–0.047 (–0.078 to –0.015)	Dominated
SA: lower sodium bicarbonate cost[f]	352.76 (–154.37 to 957.45)	–0.047 (–0.078 to –0.015)	Dominated
SA: lower inpatient stay cost[g]	539.03 (109.13 to 1050.45)	–0.046 (–0.078 to –0.015)	Dominated
SA: using the ICECAP value[h]	636.20 (187.59 to 1189.24)	–0.017 (–0.032 to 0.0001)	Dominated
SA: using the life satisfaction value[i]	580.19 (143.38 to 1130.11)	–0.396 (–0.733 to –0.059)	Dominated
Complete cases over 24 months' follow-up ($n = 114$)[j]	591.00 (166.29 to 1078.36)	–0.083 (–0.166 to –0.005)	Dominated
SA: lower sodium bicarbonate cost[f]	242.59 (–179.63 to 720.27)	–0.083 (–0.166 to –0.005)	Dominated
SA: lower inpatient stay cost[g]	593.74 (191.37 to 1072.07)	–0.083 (–0.166 to –0.005)	Dominated
SA: using the ICECAP value[h]	598.87 (215.69 to 1052.43)	–0.051 (–0.095 to –0.010)	Dominated
SA: using the life satisfaction value[i]	682.44 (257.28 to 1142.63)	–0.974 (–1.762 to –0.190)	Dominated
Complete cases over 24 months' follow-up and all participants starting renal replacement therapy during the trial ($n = 161$)[j]	808.93 (–4124.71 to 5411.89)	–0.074 (–0.151 to –0.003)	Dominated
SA: lower sodium bicarbonate cost[f]	534.61 (–4385.90 to 5149.69)	–0.074 (–0.150 to –0.003)	Dominated
SA: lower inpatient stay cost[g]	817.21 (–4097.90 to 5415.22)	–0.073 (–0.151 to –0.001)	Dominated
SA: using the ICECAP value[h,k]	422.08 (–4091.74 to 4629.60)	–0.046 (–0.090 to –0.002)	Dominated
SA: lower dialysis cost[l]	600.26 (–3560.78 to 4379.06)	–0.075 (–0.154 to –0.001)	Dominated
SA: higher dialysis cost[m]	899.41 (–4327.11 to 5714.04)	–0.074 (–0.156 to 0.002)	Dominated
SA: using the life satisfaction value[i,n]	928.18 (–4373.23 to 5729.68)	–0.072 (–1.366 to 0.002)	Dominated

ICER, incremental cost-effectiveness ratio; SA, sensitivity analysis.
a Adjusted for baseline differences (age, sex, stage of CKD, baseline EQ-5D score and baseline cost).
b Bootstrapped non-parametric 95% CI (2.5th to 97.5th percentile).
c Generalised linear model with gamma distribution and power 0.65 link function to estimate incremental costs and ordinary least squares regression to estimate incremental QALYs (complete cases).
d Generalised linear model with Gaussian distribution and power 0.5 link function to estimate incremental costs and ordinary least squares regression to estimate incremental QALYs (complete cases plus all participants starting renal replacement therapy during the trial). For incomplete cases, missing cost data were assumed to be zero and missing EQ-5D data were imputed by carrying forward the last observation. Two participants from the placebo group without EQ-5D data were excluded from the analysis.
e Applied the average cost of sodium bicarbonate (500 mg, £0.54/day).
f Applied the average cost of thrice daily generic sodium bicarbonate 500 mg with the lowest price, £0.14/day.
g Applied the average of the lower quartile unit cost for non-elective inpatient and elective inpatient bed-days (£287/day).
h Adjusted for baseline differences (age, sex, stage of CKD, baseline ICECAP value and baseline cost).
i Adjusted for baseline differences (age, sex, stage of CKD, baseline life satisfaction value and baseline cost).
j Discounted at 3.5% per year.
k Two participants from the bicarbonate group without any ICECAP data were excluded from the analysis ($n = 159$).
l Applied the average of the lower quartile unit cost for haemodialysis (£134/visit) and peritoneal dialysis (£66/visit).
m Applied the average of the upper quartile unit cost for haemodialysis (£180/visit) and peritoneal dialysis (£77/visit).
n Two participants (one from each group) without any life satisfaction data were excluded from the analysis ($n = 159$).

Figure 16 shows the scatterplot and the associated cost-effectiveness acceptability curves for the three analyses. Without the inclusion of dialysis costs, there is almost zero probability of the intervention being cost-effective at conventional thresholds of willingness to pay. For the analysis with the inclusion of renal replacement therapy costs, there is more uncertainty over cost differences, with the intervention having a probability of being cost-effective of between 0.4 and 0.1. At a willingness-to-pay threshold of £30,000 per QALY, there is a 14% probability of the intervention being deemed cost-effective.

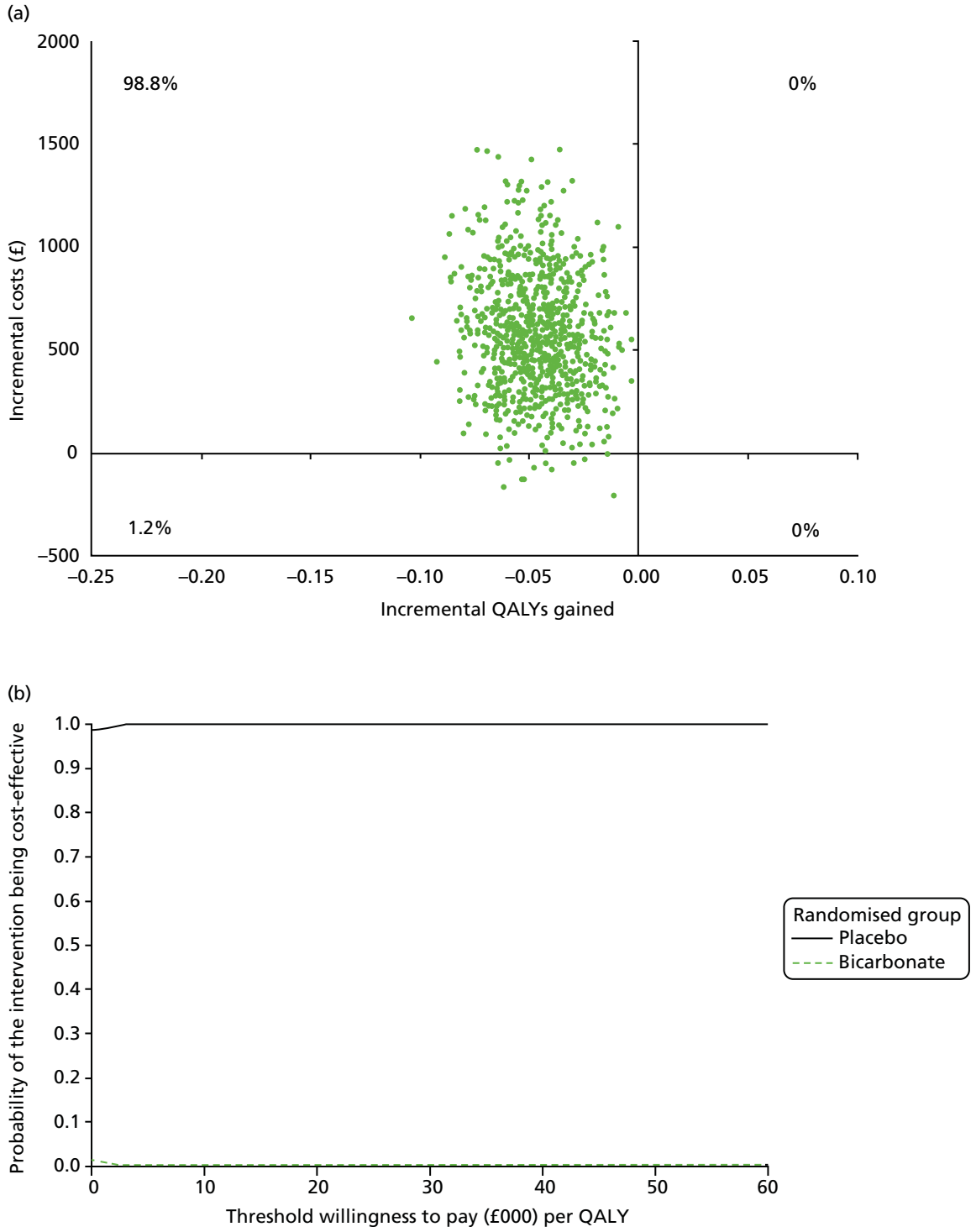

FIGURE 16 Incremental cost differences and incremental QALY differences between randomised groups. (a) Scatterplot for complete cases over 12 months' follow-up ($n = 176$); (b) cost-effectiveness acceptability curve for complete cases over 12 months' follow-up ($n = 176$); (c) scatterplot for complete cases over 24 months' follow-up ($n = 114$); (d) cost-effectiveness acceptability curve for complete cases over 24 months' follow-up ($n = 114$); (e) scatterplot for complete cases and all participants starting renal replacement therapy during the trial over 24 months' follow-up ($n = 161$); and (f) cost-effectiveness acceptability curve for complete cases and all participants starting renal replacement therapy during the trial over 24 months' follow-up ($n = 161$). (*continued*)

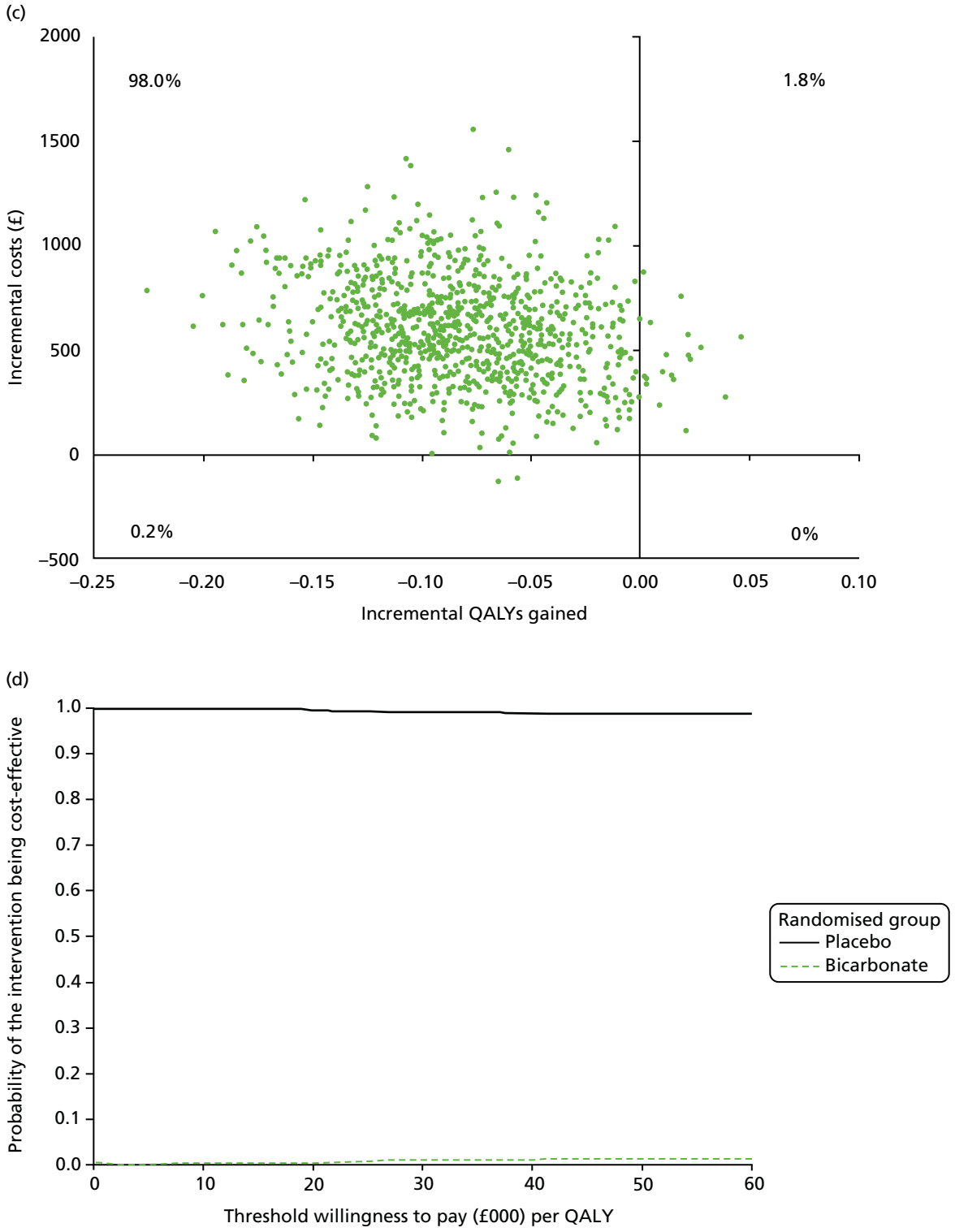

FIGURE 16 Incremental cost differences and incremental QALY differences between randomised groups. (a) Scatterplot for complete cases over 12 months' follow-up ($n = 176$); (b) cost-effectiveness acceptability curve for complete cases over 12 months' follow-up ($n = 176$); (c) scatterplot for complete cases over 24 months' follow-up ($n = 114$); (d) cost-effectiveness acceptability curve for complete cases over 24 months' follow-up ($n = 114$); (e) scatterplot for complete cases and all participants starting renal replacement therapy during the trial over 24 months' follow-up ($n = 161$); and (f) cost-effectiveness acceptability curve for complete cases and all participants starting renal replacement therapy during the trial over 24 months' follow-up ($n = 161$). (*continued*)

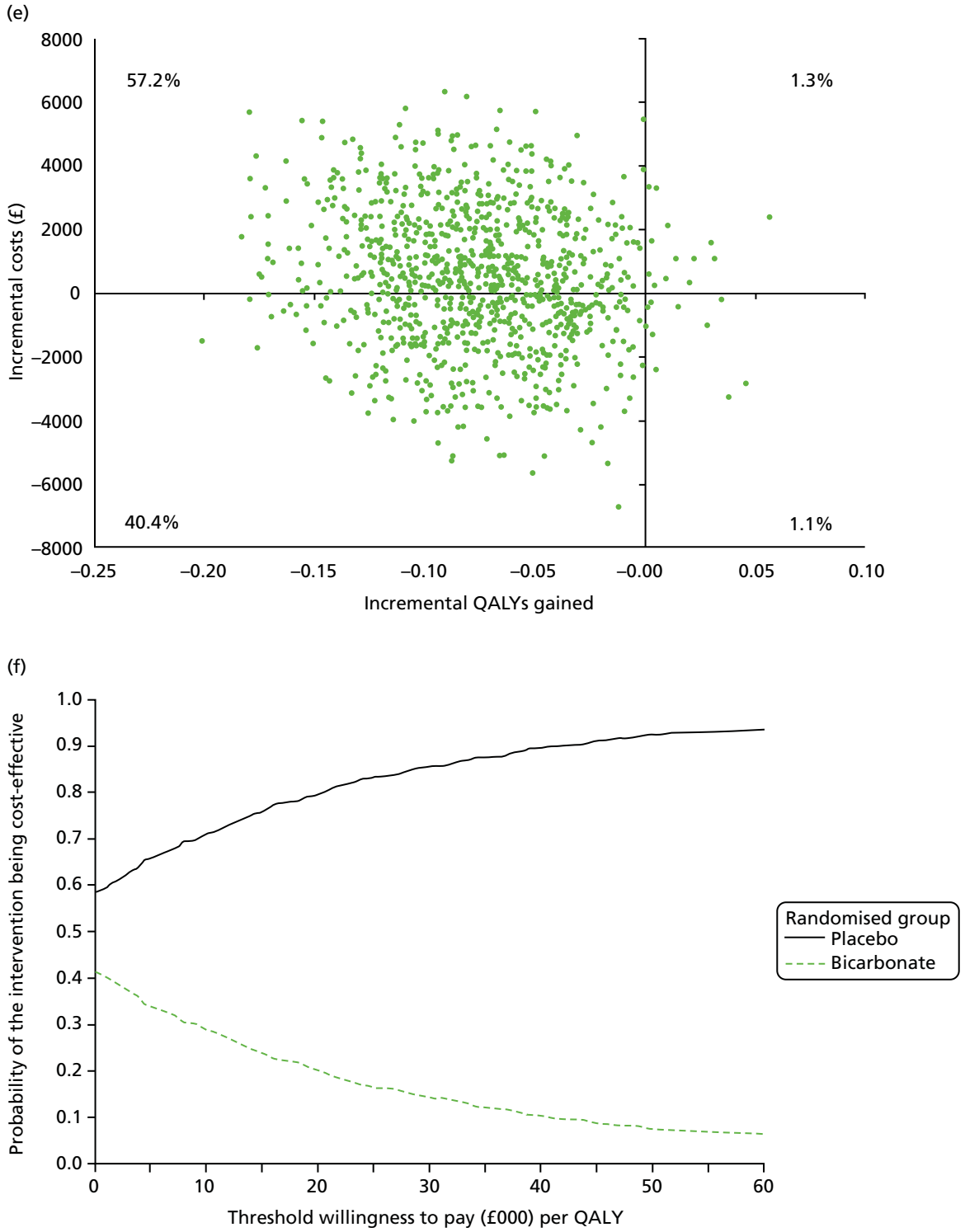

FIGURE 16 Incremental cost differences and incremental QALY differences between randomised groups. (a) Scatterplot for complete cases over 12 months' follow-up ($n = 176$); (b) cost-effectiveness acceptability curve for complete cases over 12 months' follow-up ($n = 176$); (c) scatterplot for complete cases over 24 months' follow-up ($n = 114$); (d) cost-effectiveness acceptability curve for complete cases over 24 months' follow-up ($n = 114$); (e) scatterplot for complete cases and all participants starting renal replacement therapy during the trial over 24 months' follow-up ($n = 161$); and (f) cost-effectiveness acceptability curve for complete cases and all participants starting renal replacement therapy during the trial over 24 months' follow-up ($n = 161$).

Sensitivity analyses were conducted to explore the impact of different unit cost assumptions and different quality of life weights and outcomes. First, the bicarbonate cost per day was reduced to £0.14 (the base-case value was £0.54 per day) to reflect full generic prescribing. Second, a lower inpatient cost per bed-day, using the lower bound of the interquartile range of £237, was applied (instead of £345 per day). Third, ICECAP or life satisfaction values were used as the measure of effectiveness, rather than EQ-5D values and QALYs. *Figures 17*, *28* and *29* (see *Appendix 6*) show that the impact of these changes was minimal. Placebo continued to be dominant over sodium bicarbonate, that is, costs were lower and effectiveness was higher in the placebo group, and there was an almost zero probability of treatment with sodium bicarbonate being cost-effective. *Figure 30* (see *Appendix 6*) shows that, when the participants who dropped out after commencing renal replacement therapy were added to the complete cases, there was more uncertainty over the size of the cost difference between the two groups; however, the probability of placebo being the more cost-effective treatment option was still between 80% and 90% at conventional willingness-to-pay values. These results were very robust in sensitivity analysis, even when the dialysis cost was varied.

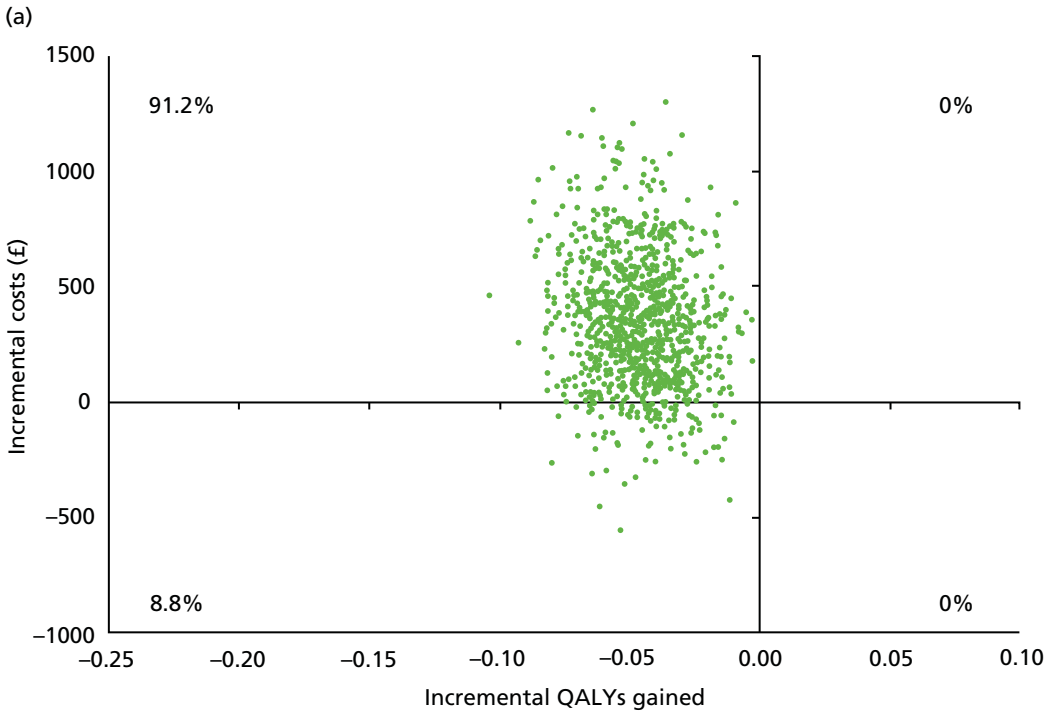

FIGURE 17 Sensitivity analyses of the incremental cost difference and incremental QALY or ICECAP difference between randomised groups: complete cases over 12 months' follow-up ($n = 176$). (a) Scatterplot for the lower sodium bicarbonate cost; (b) cost-effectiveness acceptability curve for the lower sodium bicarbonate cost; (c) scatterplot for the lower inpatient stay cost; (d) cost-effectiveness acceptability curve for the lower inpatient stay cost; and (e) scatterplot for use of ICECAP values as the measure of effectiveness. (*continued*)

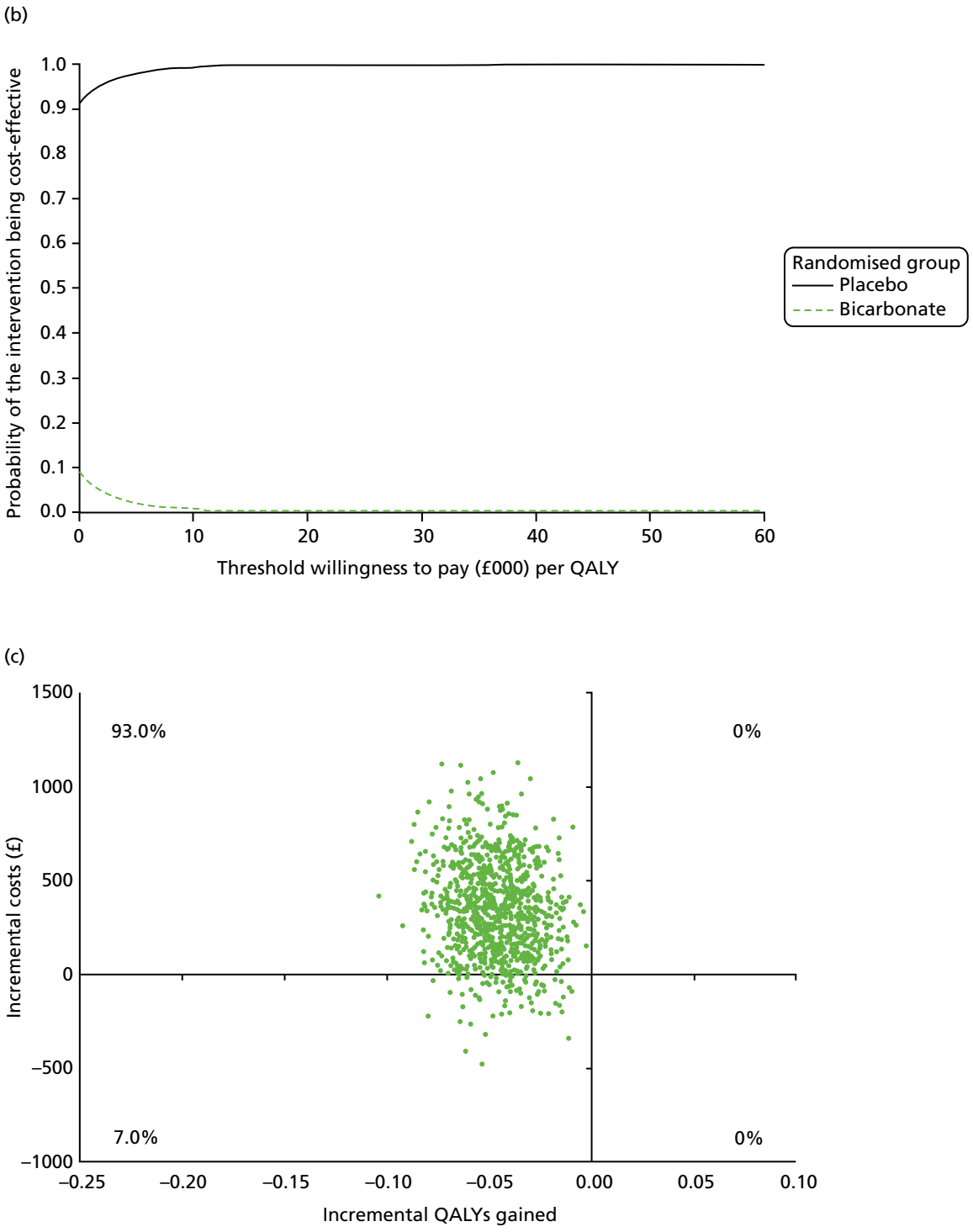

FIGURE 17 Sensitivity analyses of the incremental cost difference and incremental QALY or ICECAP difference between randomised groups: complete cases over 12 months' follow-up ($n = 176$). (a) Scatterplot for the lower sodium bicarbonate cost; (b) cost-effectiveness acceptability curve for the lower sodium bicarbonate cost; (c) scatterplot for the lower inpatient stay cost; (d) cost-effectiveness acceptability curve for the lower inpatient stay cost; and (e) scatterplot for use of ICECAP values as the measure of effectiveness. (*continued*)

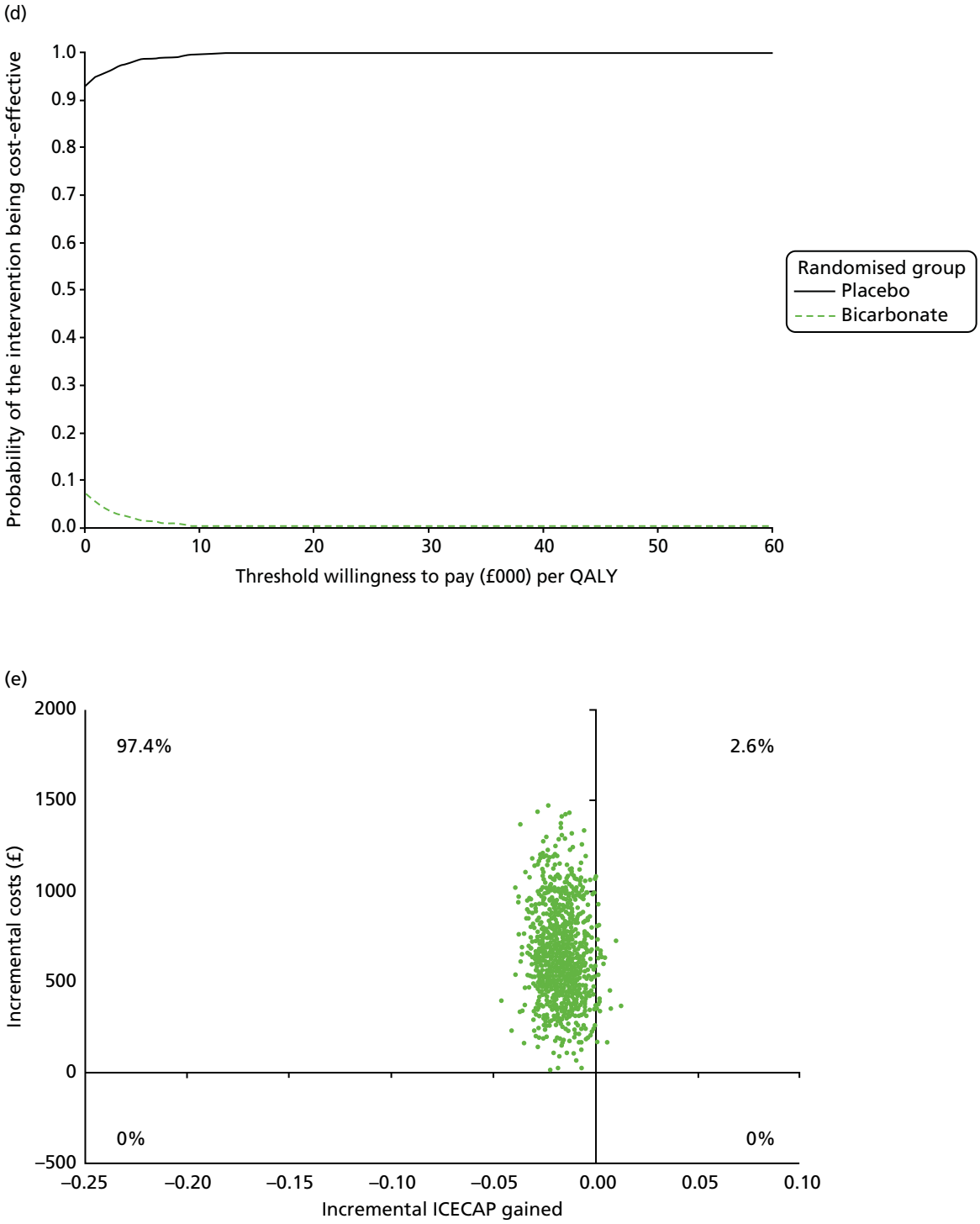

FIGURE 17 Sensitivity analyses of the incremental cost difference and incremental QALY or ICECAP difference between randomised groups: complete cases over 12 months' follow-up ($n = 176$). (a) Scatterplot for the lower sodium bicarbonate cost; (b) cost-effectiveness acceptability curve for the lower sodium bicarbonate cost; (c) scatterplot for the lower inpatient stay cost; (d) cost-effectiveness acceptability curve for the lower inpatient stay cost; and (e) scatterplot for use of ICECAP values as the measure of effectiveness.

Chapter 6 Discussion

Key findings

This pragmatic, multicentre RCT found that administration of oral sodium bicarbonate using a dose regimen similar to that currently used in UK practice did not improve physical function or quality of life or slow down deterioration of renal function compared with placebo in older people with category 4 or 5 CKD and a serum bicarbonate concentration of < 22 mmol/l. Consistent with these findings, the health economic analysis showed that treatment with bicarbonate was less cost-effective than placebo. Analyses of markers of bone and vascular health found no evidence that bicarbonate improved bone health; blood pressure was neither raised nor lowered significantly by bicarbonate therapy compared with placebo. Bicarbonate therapy was moderately well adhered to. Overall adverse event rates, including that for falls, were higher in the bicarbonate group than in the placebo group despite the two groups being balanced for most comorbidities and medications at baseline. Bicarbonate is known to cause gastrointestinal side effects, such as nausea and bloating, and this was reflected in the higher rate of gastrointestinal side effects in the intervention group. Higher rates of cardiac, respiratory and neurological adverse events were seen in the bicarbonate group, with lower rates of cancer. These differences may be the result of chance, but pooling of these data with the results from other trials of bicarbonate is required to investigate the safety profile further. The excess of cardiovascular events in the intervention group was driven by a higher rate of myocardial infarction, but the mechanism underpinning this is not clear as blood pressure was not increased in the intervention group. Fluid overload as a result of sodium load in patients with heart failure or other types of cardiovascular disease was a concern at the planning stage of the trial, but no difference in fluid overload events was seen between the two groups and decompensated heart failure events were not responsible for the observed excess of cardiovascular events.

Although rates of death and renal replacement therapy were similar in both arms, it is concerning that several measures of physical function were worse in the bicarbonate arm than in the placebo arm, despite adjusting for baseline values. Differential dropout is unlikely to explain this finding as the dropout rate was similar in each arm. Although the difference in SPPB score on repeated measures was of borderline clinical significance, the degree of difference in grip strength and 6-minute walk distance is likely to be of clinical significance.[53] These findings, in conjunction with the higher adverse event rate in the bicarbonate arm, call into question not only the efficacy but also the safety of using bicarbonate in this target patient population.

Results in context

For many of the outcomes measured in the BiCARB trial it was not possible to combine the data with those from previous trials. This was particularly the case for physical function and quality of life data, which have not been a focus of outcome measurement in previous trials. As this is the first trial to examine the effects of bicarbonate supplementation on physical function measures, it is not possible to determine if the observed worsening in physical function measures with bicarbonate is a chance finding or a real effect. Existing observational data suggest a relationship between higher serum bicarbonate concentrations and better physical function,[14,15] and a meta-analysis of studies testing the effect of bicarbonate on elite athletic performance found a weak, but significant, positive effect of bicarbonate on the performance of middle-distance athletes.[54] We were unable to find evidence of a biological mechanism that would convincingly explain why bicarbonate supplementation should worsen physical function.

Adding the results of the BiCARB trial to the meta-analysis findings showed no overall effect of bicarbonate on weight or mid-arm muscle circumference. Similarly, there was no significant worsening of systolic blood pressure with bicarbonate treatment, both overall and when confining analyses to 1-year outcomes. When combining all available trials in meta-analysis, overall estimates of the effect of oral bicarbonate therapy on serum bicarbonate levels and eGFR still suggest a modest benefit, but the results are highly heterogeneous, suggesting that the population studied in the BiCARB trial may respond differently for these outcomes from other populations studied to date, which differ in their predominant aetiology, age and ethnic background. It is also important to note that there was considerable heterogeneity in the length of follow-up, treatment schedule and whether or not patients, clinicians and study teams were masked to treatment allocation. Restricting analyses to a single time point (12 months' follow-up) removes some, but not all, of this heterogeneity. In addition, measures of variance for outcomes in some trials included in the meta-analysis were much lower than would be expected, raising the possibility that standard errors had been reported rather than standard deviations, as advertised in the papers. It is not possible to verify this without access to individual participant-level data, but the use of standard errors would lead to these trials being given undue weight in the meta-analysis results. Results from these meta-analyses should be treated with caution because of these limitations.

Generalisability and limitations with regard to generalisability

Trials of oral bicarbonate therapy to date have targeted a wide range of groups: those with serum bicarbonate concentrations in the normal range as well as those with low serum bicarbonate concentrations; those with specific renal conditions (e.g. CKD of unknown origin, hypertensive nephropathy with albuminuria); and those with moderate renal disease (CKD category 3), which is not a usual target for bicarbonate therapy. This trial is distinctive in targeting older people, who make up the majority of patients with CKD in the UK and most other high-income countries. It included patients from across the UK with advanced CKD (thus reflecting the usual target group for bicarbonate therapy in practice).

The increase in serum bicarbonate concentration seen in the bicarbonate arm compared with the placebo arm was modest and it could be argued that the lack of benefit with regard to the main study outcomes is unsurprising given this modest increment in serum bicarbonate concentration. However, the increase in serum bicarbonate concentration was consistent with that seen in previous trials, including a recent trial published only in abstract form,[55] albeit at the lower end of the range of responses seen. Furthermore, several trials demonstrating larger increases in serum bicarbonate concentration used an open-label design and titrated treatment to reach specific bicarbonate targets. In current UK practice, doses of 1.5–3 g per day of oral bicarbonate are commonly used and our treatment strategy reflected this practice. Although we cannot therefore rule out a beneficial effect of higher doses of bicarbonate, our results support the contention that current UK practice for bicarbonate replacement in CKD does not improve a wide range of outcomes in older patients with advanced CKD. Increasing the dose of sodium bicarbonate beyond 3 g per day risks further worsening of adherence, as bicarbonate tablets are large and difficult for older people to swallow. In addition, higher doses run the risk of increasing the rate of adverse events still further, particularly gastrointestinal side effects. Nevertheless, treatment regimens (using either bicarbonate or newer acid-binding agents) that produce greater increases in serum bicarbonate concentration could provide benefits and require testing.

The commissioning brief and trial design focused on patients with a mild degree of acidosis. Few participants with a serum bicarbonate concentration of < 18 mmol/l were enrolled, as most patients with a serum bicarbonate concentration this low are already being treated with bicarbonate. We are therefore unable to comment on the potential benefits of treating more severe levels of acidosis in this population.

Other limitations

One of the key limitations of this study is the high proportion of white participants. One previous UK trial[23] that showed positive effects of oral sodium bicarbonate treatment enrolled predominantly participants of South Asian and African ethnicity – there was an insufficient number of participants to exclude a beneficial effect in these ethnic groups. The trial enrolled a preponderance of men, which may limit the generalisability of the results, given the relative under-representation of women. The study population had relatively stable CKD, with low rates of progression to end-stage kidney disease, and this was consistent with the low levels of proteinuria in the study population.

The original target for recruitment in this trial (380 participants) was not reached, despite participants being recruited from 27 UK sites. This was, in part, because of a lack of clinical equipoise; surveys of UK practitioners performed by the trial team during the trial suggested that most nephrologists were treating mild degrees of acidosis with bicarbonate already, thus reducing the pool of eligible participants. Despite this, revised sample size calculations performed to inform the decision to cease recruitment suggested that the sample size randomised ($n = 300$) had 87% power to detect a 1-point difference in the primary outcome of change in SPPB score. Our results exclude a 1-point improvement in the primary outcome by a wide margin and also exclude a more conservative 0.5-point improvement (posited by some researchers as the MCID for the SPPB[53]).

Bicarbonate levels in the placebo group increased gradually over time, which reduced the difference in bicarbonate levels between the groups. Some of this increase is likely to have been the result of regression to the mean and some is likely to have been the result of the dropout of participants who started renal replacement therapy (who were more likely to have worse renal function and worse acidosis), but some may also have been the result of individuals in the placebo group stopping the study medication and starting unblinded bicarbonate therapy as part of routine practice. However, the impact of starting unblinded bicarbonate therapy is likely to have been small as only 18 participants in the placebo group stopped the study medication to start unblinded therapy.

The majority of participants who commenced renal replacement therapy were lost to follow-up at the point of commencing renal replacement therapy. The costs of ongoing renal replacement therapy for these participants could not be directly captured as part of the main health economics analysis, and quality of life after starting renal replacement therapy was also not ascertained for participants who dropped out of the trial. Renal replacement therapy costs were included in one of the economic analyses but other associated costs for patients who dropped out were not captured. The same number of participants commenced renal replacement therapy in each arm (33 in each arm), with the time to commencement of therapy being slightly shorter in the bicarbonate arm. The economic analysis is consistent with this finding, with overall costs higher in the bicarbonate arm. It is possible that unmeasured costs associated with, but not attributable to, renal replacement therapy (e.g. additional inpatient stays, additional adverse events) could influence the economic analysis. However, the fact that more adverse events were seen during the trial in the bicarbonate arm suggests that any unmeasured events would tend to accentuate, rather than reverse, the results of the health economic analysis as presented. Similarly, small differences between the groups in the time spent avoiding the commencement of renal replacement therapy are likely to have large effects on costs. However, the analysis of time to commencement of renal replacement therapy suggests that participants in the bicarbonate group started renal replacement sooner, and the addition of these renal replacement costs reinforced, rather than overturned, the results of the main economic analyses.

Strengths

The key strengths of this trial were its comparatively large size; adequate follow-up time; participant, clinician and researcher masking; and broad inclusion criteria. In contrast to almost all previous trials, our use of a placebo control reduced the opportunities for bias, particularly with respect to decision-making

around the timing of commencement of renal replacement therapy. An additional key strength was the broad range of outcome measures examined, with a particular focus on physical function and quality of life. These are the outcomes that older people report are the most important to them, and this focus is of particular importance in this group of patients with extensive multimorbidity. A narrow focus on a single disease – even in patients with advanced CKD – is inappropriate in this group, and considering physical function and quality of life enables an assessment of the overall benefit of treatment to patients in a way that organ-specific measures do not.

Chapter 7 Conclusions

Implications for health care

Bicarbonate therapy is currently in widespread use to treat mild degrees of acidosis in patients with stage 4 or 5 CKD. This is largely based on observational data suggesting an association between acidosis and a range of deleterious outcomes, including accelerated decline in renal function and adverse bone health, physical function and vascular health. There is little trial evidence to support current practice, a state of affairs that is acknowledged in guidelines.[31,32] Our results suggest that, at least in this predominantly male and white population of older patients with CKD category 4 and 5, 1.5–3 g per day of oral bicarbonate did not produce any health benefits and may be associated with net harms compared with placebo. Although other indications for the control of acidosis exist (e.g. high potassium concentrations), evidence from the current trial suggests that the additional cost, treatment burden and side effects of oral bicarbonate therapy may not justify its use in older people with advanced CKD and mild acidosis.

Suggestions for future research

A number of other trials of bicarbonate therapy are currently in progress or are in the process of being published.[55–57] These trials have targeted a range of CKD severities (CKD category 3b–5) and a range of entry serum bicarbonate concentrations (< 21 mmol/l, > 18 mmol/l and 20–25 mmol/l); in two of the trials, a strategy of dose adjustment to keep the serum bicarbonate concentration at > 24 mmol/l has been employed. None of these trials targets older people as a specific group. We recommend that the key research priority should be to combine data from these trials once they are available. We therefore make the following suggestions for further research:

- An individual participant meta-analysis should be conducted, examining the effects of bicarbonate therapy on physical function, quality of life, renal function and progression to renal replacement therapy, anthropometric measurements and bone and vascular health.
- Importantly, such a meta-analysis should also seek to pool adverse events, particularly cardiovascular events, and to identify the characteristics of those most likely to respond to bicarbonate therapy.
- The results from the BiCARB trial call into question the usefulness of bicarbonate therapy in other groups in whom it is currently used routinely. Depending on the results of meta-analyses, it may be necessary to formally test the effectiveness of bicarbonate therapy in other groups with CKD, for example younger patients.
- Alternative methods to manage acidosis in advanced CKD should be tested. A pilot study of dose titration to target would be one way to approach low bicarbonate levels once it is clearer which subgroups (if any) are more likely to benefit. Novel methods of managing acidosis, such as use of non-absorbed hydrochloric acid binders, also require testing.

A final recommendation is that clinical trials in disease areas that affect predominantly older people should be designed and executed in such a way that older people are well represented and should use outcome measures that are important to older people.[58] The BiCARB trial shows how this can be successfully achieved in the field of CKD; there is a need to ensure that similar outcomes and methods are used to answer other questions within the field of CKD, but also more widely in other organ-specific fields of clinical practice. The evidence base underpinning the design and delivery of trials that are appropriate for older people is very limited; research is needed on how best to design trials in older people, how to recruit and retain older people successfully and the use of outcomes that are relevant to older people with multimorbidity.

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Publications

Witham MD, Band MM, Littleford RC, Avenell A, Soiza RL, McMurdo ME, *et al.* Does oral sodium bicarbonate therapy improve function and quality of life in older patients with chronic kidney disease and low-grade acidosis (the BiCARB trial)? Study protocol for a randomized controlled trial. *Trials* 2015;**16**:326.

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Data-sharing statement

All data requests should be addressed to the corresponding author or the trial sponsor for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Search strategy for the systematic review: MEDLINE search

Date range searched: inception to October 2018.

Search strategy

1. exp BICARBONATES [MESH] (24,176)
2. exp Sodium bicarbonate [MESH] (4387)
3. Bicarbonates [mp] (21,707)
4. 1 or 2 or 3 (24,458)
5. Chronic kidney disease [mp] (43,554)
6. Renal insufficiency, chronic [MESH] (17,753)
7. CKD [mp] (24,465)
8. Kidney failure, chronic [MESH] (89,084)
9. 5 or 6 or 7 or 8 (129,377)
10. 4 and 9 (826)
11. Limit 10 to (English language and RCT) (77)

Appendix 2 Systematic review findings

TABLE 23 Characteristics of included studies

Study	Location	*n*	Mean age (years)	CKD category	Bicarbonate level entry criterion	Intervention	Comparator	Duration	Primary outcome
Mathur 2006[22]	India	40	41	'Mild to moderate' CKD (creatinine < 442 µmol/l). CKD category not specified	Not specified	1.2 mEq/kg of oral bicarbonate in three divided doses, titrated to maintain serum bicarbonate in the range 22–26 mmol/l	Placebo	3 months	Not specified
de Brito-Ashurst 2009[23]	UK	134	55	4 or 5	Bicarbonate > 16 mmol/l and < 19 mmol/l	600 mg of oral bicarbonate three times per day, increased as needed to maintain serum bicarbonate at > 23 mmol/l	Usual care	2 years	Decline in creatinine clearance of > 3 ml/minute/year
Mahajan 2010[24]	USA	120	51	2, with hypertension and macroalbuminuria	Total CO_2 > 24.5 mmol/l	0.5 mEq/kg lean body weight of oral bicarbonate	Placebo	5 years	Decline in eGFR decline
Jeong 2014[26]	Republic of Korea	80	55	4 or 5	Total CO_2 < 22 mmol/l	1 g of oral bicarbonate three times per day, titrated to maintain serum bicarbonate at > 22 mmol/l	Usual care	12 months	eGFR
Goraya 2014[25]	USA	108	54	3	Total CO_2 > 22 mmol/l and < 24 mmol/l	0.3 mEq/kg lean body weight of oral bicarbonate in three divided doses	Usual care	3 years	eGFR
Bellasi 2016[27]	Italy	145	65	3b or 4, in patients with type 2 diabetes mellitus	Bicarbonate < 24 mmol/l	0.5 mEq/kg of oral bicarbonate twice daily, until serum bicarbonate is in the range 24–28 mmol/l	Usual care	12 months	Insulin resistance
Dubey 2018[28]	India	188	50	3 and 4	Bicarbonate < 22 mmol/l	Oral bicarbonate titrated with weekly monitoring	Usual care	6 months	Mid-arm muscle circumference

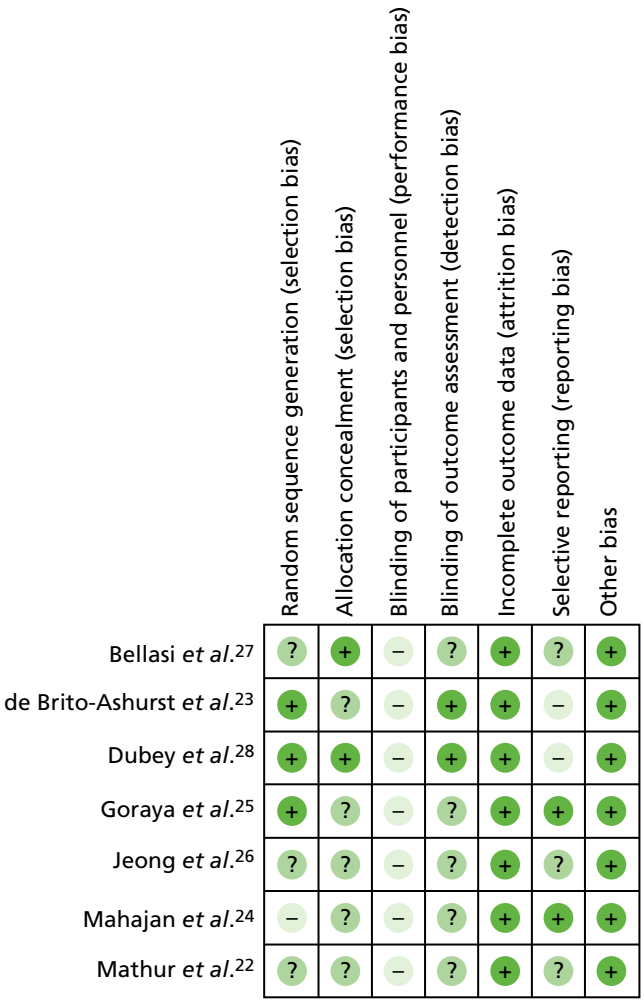


FIGURE 18 Quality assessment of included studies.

Meta-analysed outcomes, before reporting of the BiCARB trial results

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
Mathur *et al.*[22]	22.93	7.12	20	17.89	4.67	20	8.0	5.04 (1.31 to 8.77)	2006
de Brito-Ashurst *et al.*[23]	25	4	62	20	4	67	14.3	5.00 (3.62 to 6.38)	2009
Mahajan *et al.*[24]	26.4	0.6	37	26.1	0.8	34	16.3	0.30 (–0.03 to 0.63)	2010
Goraya *et al.*[25]	24	0.6	36	22.4	0.6	36	16.3	1.60 (1.32 to 1.88)	2014
Jeong *et al.*[26]	1.28	3.56	37	–2.42	3.82	36	13.5	3.70 (2.01 to 5.39)	2014
Bellasi *et al.*[27]	26	2	71	22.3	1.9	74	15.9	3.70 (3.06 to 4.34)	2016
Dubey *et al.*[28]	23.45	2.72	88	17.8	2.47	89	15.7	5.65 (4.88 to 6.42)	2018
Total (95% CI)			351			356	100.0	3.40 (1.93 to 4.88)	

Heterogeneity: $\tau^2 = 3.45$; $\chi^2 = 239.76$, df = 6 ($p < 0.00001$); $I^2 = 97\%$

Test for overall effect: $z = 4.53$ ($p < 0.00001$)

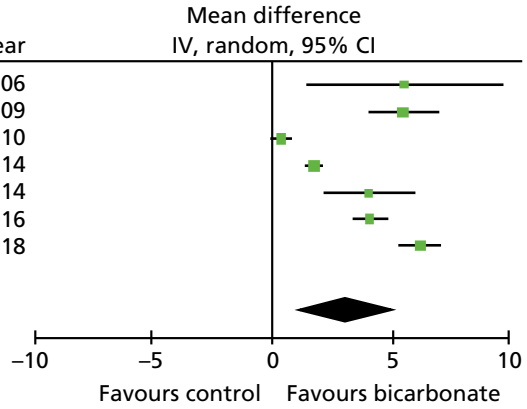


FIGURE 19 Serum bicarbonate concentration (mmol/l) (any time point). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
de Brito-Ashurst *et al.*[23]	22	4	62	20	3	67	32.0	2.00 (0.77 to 3.23)	2009
Jeong *et al.*[26]	1.28	3.56	37	–2.42	3.82	36	23.9	3.70 (2.01 to 5.39)	2014
Bellasi *et al.*[27]	26	2	71	22.3	1.9	74	44.1	3.70 (3.06 to 4.34)	2016
Total (95% CI)			170			177	100.0	3.16 (2.02 to 4.29)	

Heterogeneity: $\tau^2 = 0.66$; $\chi^2 = 5.96$, df = 2 ($p = 0.05$); $I^2 = 66\%$

Test for overall effect: $z = 5.44$ ($p < 0.00001$)

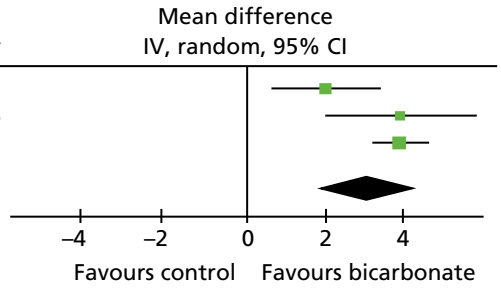


FIGURE 20 Serum bicarbonate concentration (mmol/l) (1-year follow-up only). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
de Brito-Ashurst *et al.*[23]	20	6	62	20	6	67	19.5	0.00 (–2.07 to 2.07)	2009
Mahajan *et al.*[24]	67.6	4.9	37	64	6.1	34	17.0	3.60 (1.01 to 6.19)	2010
Goraya *et al.*[25]	35.2	6.9	36	28.8	7.3	36	14.1	6.40 (3.12 to 9.68)	2014
Jeong *et al.*[26]	–2.03	3.39	37	–4.84	5.15	36	19.8	2.81 (0.80 to 4.82)	2014
Bellasi *et al.*[27]	32	15	71	31	16	74	8.7	1.00 (–4.05 to 6.05)	2016
Dubey *et al.*[28]	32.7	5.94	88	28.2	5.94	89	21.0	4.50 (2.75 to 6.25)	2018
Total (95% CI)			331			336	100.0	3.10 (1.29 to 4.92)	

Heterogeneity: $\tau^2 = 3.29$; $\chi^2 = 15.82$, df = 5 ($p = 0.007$); $I^2 = 68\%$

Test for overall effect: $z = 3.35$ ($p = 0.0008$)

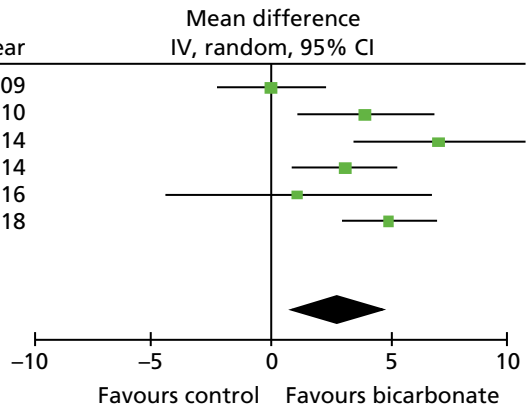


FIGURE 21 Estimated GFR (ml/minute/1.73 m²) (any time point). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
de Brito-Ashurst *et al.*[23]	20	6	62	20	6	67	42.6	0.00 (–2.07 to 2.07)	2009
Jeong *et al.*[26]	–2.03	3.39	37	–4.84	5.15	36	43.8	2.18 (0.80 to 4.82)	2014
Bellasi *et al.*[27]	32	15	71	31	16	74	13.6	1.00 (–4.05 to 6.05)	2016
Total (95% CI)			170			177	100.0	1.37 (–0.69 to 3.43)	

Heterogeneity: $\tau^2 = 1.48$; $\chi^2 = 3.68$, df = 2 ($p = 0.16$); $I^2 = 46\%$

Test for overall effect: $z = 1.30$ ($p = 0.19$)

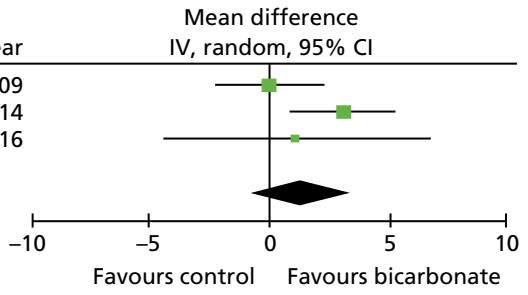


FIGURE 22 Estimated GFR (ml/minute/1.73 m²) (1-year follow-up only). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
Mathur *et al.*[22]	140	4	20	134	4	20	25.0	6.00 (3.52 to 8.48)	2006
Mahajan *et al.*[24]	135.1	6.2	37	133.3	8.1	34	21.9	1.80 (–1.58 to 5.18)	2010
Goraya *et al.*[25]	135.7	4.5	36	135.4	6.2	36	24.9	0.30 (–2.20 to 2.80)	2014
Bellasi *et al.*[27]	125	17	71	121	16	74	15.6	4.00 (–1.38 to 9.38)	2016
Dubey *et al.*[28]	124	24.73	88	128	19.79	89	12.6	–4.00 (–10.60 to 2.60)	2018
Total (95% CI)			252			253	100.0	2.09 (–1.00 to 5.18)	

Heterogeneity: $\tau^2 = 8.35$; $\chi^2 = 14.78$, df = 4 ($p = 0.005$); $I^2 = 73\%$

Test for overall effect: $z = 1.33$ ($p = 0.19$)

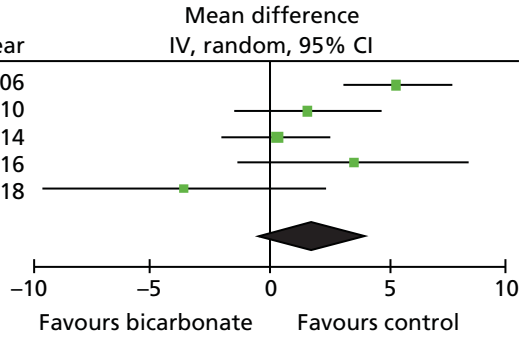


FIGURE 23 Systolic blood pressure (mmHg) (any time point). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
Mathur *et al.*[22]	58.4	1.2	20	59.4	0.9	20	28.4	–1.00 (–1.66 to –0.34)	2006
Goraya *et al.*[25]	83.9	5.9	36	81.2	6	36	11.4	2.70 (–0.05 to 5.45)	2014
Jeong *et al.*[26]	0.64	2.6	37	–0.12	2.59	36	23.5	0.76(–0.43 to 1.95)	2014
Bellasi *et al.*[27]	76.3	12.8	71	73.4	15	74	5.4	2.90 (–1.63 to 7.43)	2016
Dubey *et al.*[28]	54.1	0.35	88	53.3	0.3	89	31.2	0.80 (0.70 to 0.90)	2018
Total (95% CI)			252			255	100.0	0.61 (–0.55 to 1.77)	

Heterogeneity: $\tau^2 = 1.12$; $\chi^2 = 30.96$, df = 4 ($p < 0.00001$); $I^2 = 87\%$

Test for overall effect: $z = 1.03$ ($p = 0.30$)

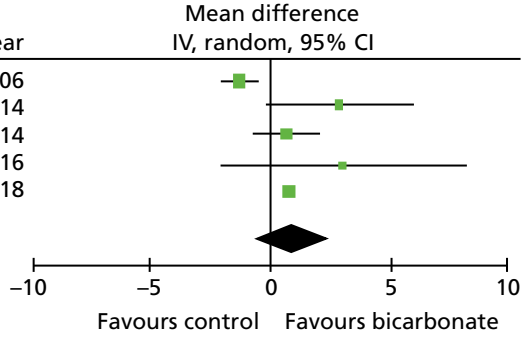


FIGURE 24 Weight (kg) (any time point). IV, instrumental variable; SD, standard deviation.

Study or subgroup	Bicarbonate Mean	SD	Total (*n*)	Control Mean	SD	Total (*n*)	Weight (%)	Mean difference IV, random, 95% CI	Year
de Brito-Ashurst *et al.*[23]	26.3	0.6	62	24.5	0.5	67	35.1	1.80 (1.61 to 1.99)	2009
Jeong *et al.*[26]	0.28	2.37	37	0.31	1.74	36	29.6	–0.03 (–0.98 to 0.92)	2014
Dubey *et al.*[28]	22.8	0.05	88	22.6	0.05	89	35.3	0.20 (0.19 to 0.21)	2018
Total (95% CI)			187			192	100.0	0.69 (–0.60 to 1.98)	

Heterogeneity: $\tau^2 = 1.22$; $\chi^2 = 267.07$, df = 2 ($p < 0.00001$); $I^2 = 99\%$

Test for overall effect: $z = 1.05$ ($p = 0.29$)

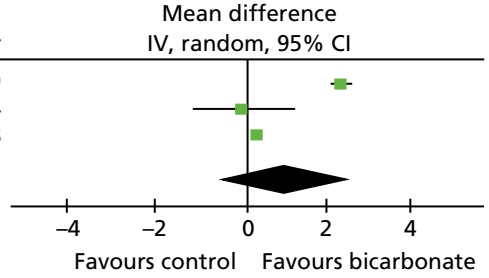


FIGURE 25 Mid-arm muscle circumference (cm) (any time point). IV, instrumental variable; SD, standard deviation.

Appendix 3 List of secondary outcomes in the BiCARB trial and details of tests used

Test	Test details
6-minute walk distance	Measured on a 25-m course with standardised encouragement
Handgrip strength	Maximum value in the dominant hand to the nearest 0.1 kg (best of three). Measured using a Takei Grip-D dynamometer (Takei Scientific Instruments Co Ltd. Niigata City, Japan)
Weight	To nearest 0.1 kg
Mid-arm muscle circumference	Calculated as mid-arm circumference in cm – (π × triceps skinfold thickness in cm)
Triceps skinfold thickness	Using callipers, measured to nearest mm
Mid-thigh circumference	To nearest 0.1 cm, measured using a tape measure
EQ-5D-3L score	Collected using standard published questionnaire. Results mapped to UK preference weights before analysis
EQ-5D thermometer	Collected using standard published questionnaire
KDQoL questionnaire	Collected using standard published questionnaire
eGFR	Derived from serum creatinine concentration via the MDRD4 equation
Creatinine	Analysed by local NHS laboratories at each site
Cystatin C	Analysed by central laboratory (Canterbury) using a turbidimetric immunoassay (Abbott ARCHITECT analyser, Maidenhead, UK). Analytical CVs: 4.7%, 1.8% and 1.5% at concentrations of 63, 170 and 645 µmol/l, respectively
Urinary albumin/creatinine ratio	Analysed by central laboratory (Canterbury). Urinary albumin measured using a turbidimetric immunoassay and urinary creatinine measured using an enzymatic assay, both on an Abbott ARCHITECT analyser. Albumin – analytical CVs: 6.4% and 2.5% at concentrations of 23.3 and 72.2 mg/l, respectively; creatinine – analytical CVs: 1.1% and 0.9% at concentrations of 5.3 and 11.3 mmol/l, respectively
Tartrate-resistant acid phosphatase-5b	Analysed by central laboratory (Dundee) using an enzyme-linked immunosorbent assay (CUSABIO, Houston, TX, USA). Intra-assay CVs: 14.3% using plasma pool, 6.3% using 2.5 mIU/ml standard; inter-assay CV: 6.9% using plasma pool
Bone-specific alkaline phosphatase	Analysed by central laboratory (Dundee) using a sandwich chemiluminescence assay (DiaSorin, Saluggia, Italy). Mean intra-assay CV: 9.1% using plasma pool; inter-assay CV: 8.5–11.5% using control standards
PTH	Analysed by local NHS laboratories at each site
25-hydroxyvitamin D	Analysed by central laboratory (Guy's and St Thomas') using a Chemiflex Chemiluminescence Microparticle Immunoassay (Abbott Diagnostics, Lake Forest, IL, USA). Inter-assay CVs: 6.6%, 4% and 3% at serum 25-hydroxyvitamin D concentrations of 13, 25 and 50 nmol/l, respectively
1,25-dihydroxyvitamin D	Analysed by central laboratory (Guy's and St Thomas'). Immunoextraction followed by chemiluminescence immunoassay on an IDS-iSYS system (Immunodiagnostic Systems Holdings plc, Boldon, UK). Inter-assay CVs: 9.5% and 10.25% at 1,25-dihydroxyvitamin D concentrations of 58 and 103 pmol/l, respectively
N-terminal pro-B-type natriuretic peptide	Analysed by central laboratory (Dundee) using an enzyme-linked immunosorbent assay (Meso Scale Discovery, Rockville, MD, USA). Mean intra-assay CVs: 4.7% across all samples, 9.2–11.7% using control standards; inter-assay CV: 2.3–5.3% using control standards
Haemoglobin	Analysed by local NHS laboratories at each site
Total cholesterol	Analysed by local NHS laboratories at each site

APPENDIX 3

Test	Test details
Serum albumin	Analysed by local NHS laboratories at each site
Thyroid-stimulating hormone	Analysed by local NHS laboratories at each site
Serum potassium	Analysed by local NHS laboratories at each site
Serum calcium	Adjusted for serum albumin concentration. Analysed by local NHS laboratories at each site
Serum phosphate	Analysed by local NHS laboratories at each site
HbA_{1c}	Analysed by local NHS laboratories at each site
Serum bicarbonate	Analysed by local NHS laboratories at each site
Systolic blood pressure Diastolic blood pressure	Measured using an OMRON 705CP-II (HEM-759-E2) (Omron Healthcare UK Ltd, Milton Keynes, UK) oscillometric device. Three readings supine were carried out after 5 minutes' rest; the mean of the second and third readings was used as the blood pressure reading
Falls	Collected using monthly self-report diaries

CV, coefficient of variation.

Appendix 4 Unit costs for the health economic analysis

TABLE 24 Unit costs applied to value NHS health-care resource use (2016/17 UK prices)

Resource	Unit	Source	Basis of estimate	Cost (£)
Inpatient stay	Day	*NHS Reference Costs 2016–17*[59]	Non-elective inpatient and elective inpatient stays (mean cost over these two categories)	345
Day case	Visit	*NHS Reference Costs 2016–17*[59]	Day case	736
Outpatient: nephrology	Visit	*NHS Reference Costs 2016–17*[59]	WF01A Non-Admitted Face-to-Face Attendance, Follow-up 361 Nephrology, WF01B Non-Admitted Face-to-Face Attendance, First 361 Nephrology (mean of consultant-led and non-consultant-led attendance)	150
Outpatient: other	Visit	*NHS Reference Costs 2016–17*[59]	Outpatient Attendances (weighted average of all outpatient attendances)	120
Haemodialysis	Visit	*NHS Reference Costs 2016–17*[59]	LD01A Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, ≥ 19 years, LD02A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, ≥ 19 years, LD02A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, ≥ 19 years, LD03A Hospital Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, ≥ 19 years, LD04A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, ≥ 19 years, LD05A Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, ≥ 19 years, LD06A Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, ≥ 19 years, LD07A Satellite Haemodialysis or Filtration, with Access via Haemodialysis Catheter, with Blood-Borne Virus, ≥ 19 years, LD08A Satellite Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, with Blood-Borne Virus, ≥ 19 years, LD09A Home Haemodialysis or Filtration, with Access via Haemodialysis Catheter, ≥ 19 years, LD10A Home Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, ≥ 19 years (mean cost over these 10 categories)	167
Peritoneal dialysis	Session	*NHS Reference Costs 2016–17*[59]	LD11A Continuous Ambulatory Peritoneal Dialysis, ≥ 19 years, LD12A Automated Peritoneal Dialysis, ≥ 19 years, LD13A Assisted Automated Peritoneal Dialysis, ≥ 19 years (mean cost over these three categories)	76
Renal transplant	Episode	*NHS Reference Costs 2016–17*[59]	LA01A Kidney Transplant, ≥ 19 years, from Cadaver Non-Heart-Beating Donor, LA02A Kidney Transplant, ≥ 19 years, from Cadaver Heart-Beating Donor, LD03A Kidney Transplant, ≥ 19 years, from Live Donor (mean cost over these three categories)	12,681
Day hospital	Visit	*NHS Reference Costs 2016–17*[59]	DCFRAD Day Care Facilities Regular Attendances, Elderly Patients	132
Day centre	Visit	Curtis and Burns[60]	Local authority own provision day care for older people	63
GP	Visit	Curtis and Burns[60]	9.22-minute consultation, including qualification and direct staff	38

continued

TABLE 24 Unit costs applied to value NHS health-care resource use (2016/17 UK prices) (*continued*)

Resource	Unit	Source	Basis of estimate	Cost (£)
Home help/ professional home carer	Visit	Curtis and Burns[60]	Assume visit lasts 30 minutes.[61] Face-to-face, independent sector home care provided for social services (weighted mean over weekday, daytime weekend, night-time weekday and night-time weekend)	15
District nurse	Visit	*NHS Reference Costs 2016–17*[59]	N02AF District Nurse, Adult, Face-to-Face	37
Physiotherapist	Visit	*NHS Reference Costs 2016–17*[59]	WF01A Non-Admitted Face-to-Face Attendance, Follow up 650 Physiotherapy, WF01B Non-Admitted Face-to-Face Attendance, First 650 Physiotherapy, AHP Allied Health Professionals A08A1 Physiotherapist, Adult, One to One, AHP Allied Health Professionals A08AG Physiotherapist, Adult, Group (mean over these four categories)	52
Occupational therapist	Visit	*NHS Reference Costs 2016–17*[59]	WF01A Non-Admitted Face-to-Face Attendance, Follow up 651 Occupational Therapy, WF01B Non-Admitted Face-to-Face Attendance, First 651 Occupational Therapy, AHP Allied Health Professionals A06A1 Occupational Therapist, Adult, One to One, AHP Allied Health Professionals A06AG Occupational Therapist, Adult, Group (mean cost over these four categories)	72
Speech therapist	Visit	*NHS Reference Costs 2016–17*[59]	WF01A Non-Admitted Face-to-Face Attendance, Follow up 652 Speech and Language Therapy, WF01B Non-Admitted Face-to-Face Attendance, First 651 Speech and Language Therapy, AHP Allied Health Professionals A13A1 Speech and Language Therapist, Adult, One to One, AHP Allied Health Professionals A13AG Speech and Language Therapist, Adult, Group (mean cost over these four categories)	101

Appendix 5 Recruitment

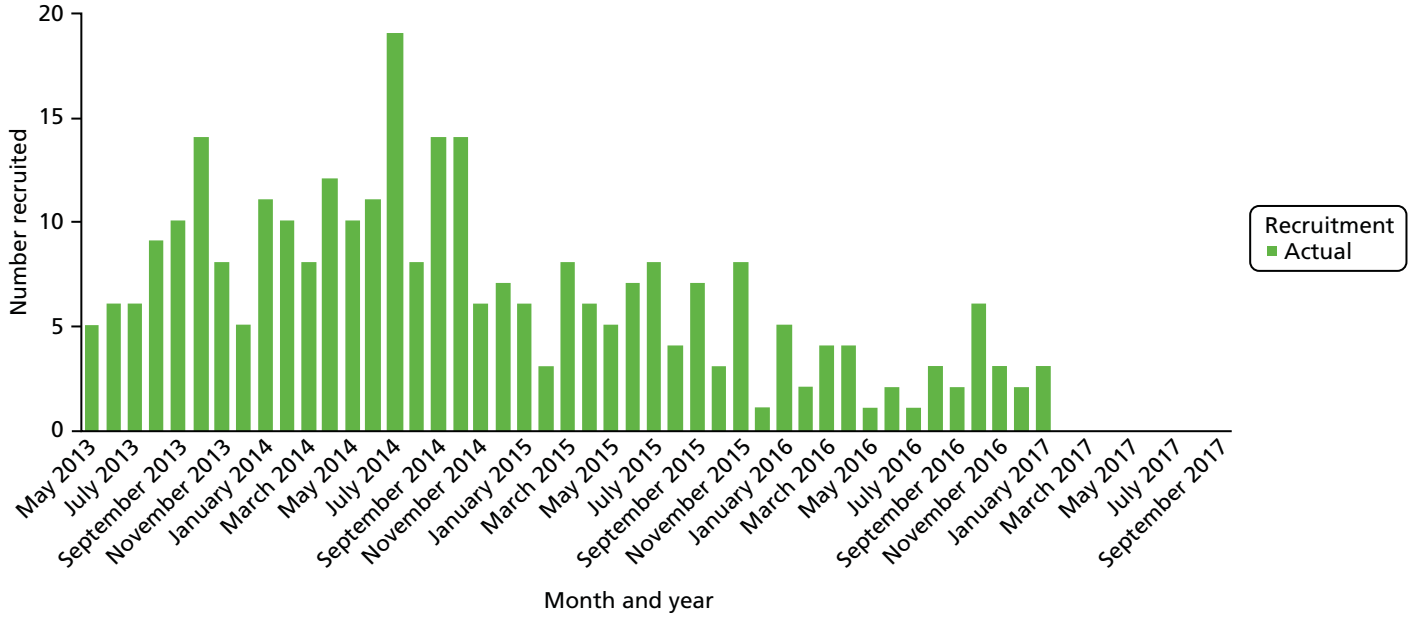


FIGURE 26 Monthly recruitment rate.

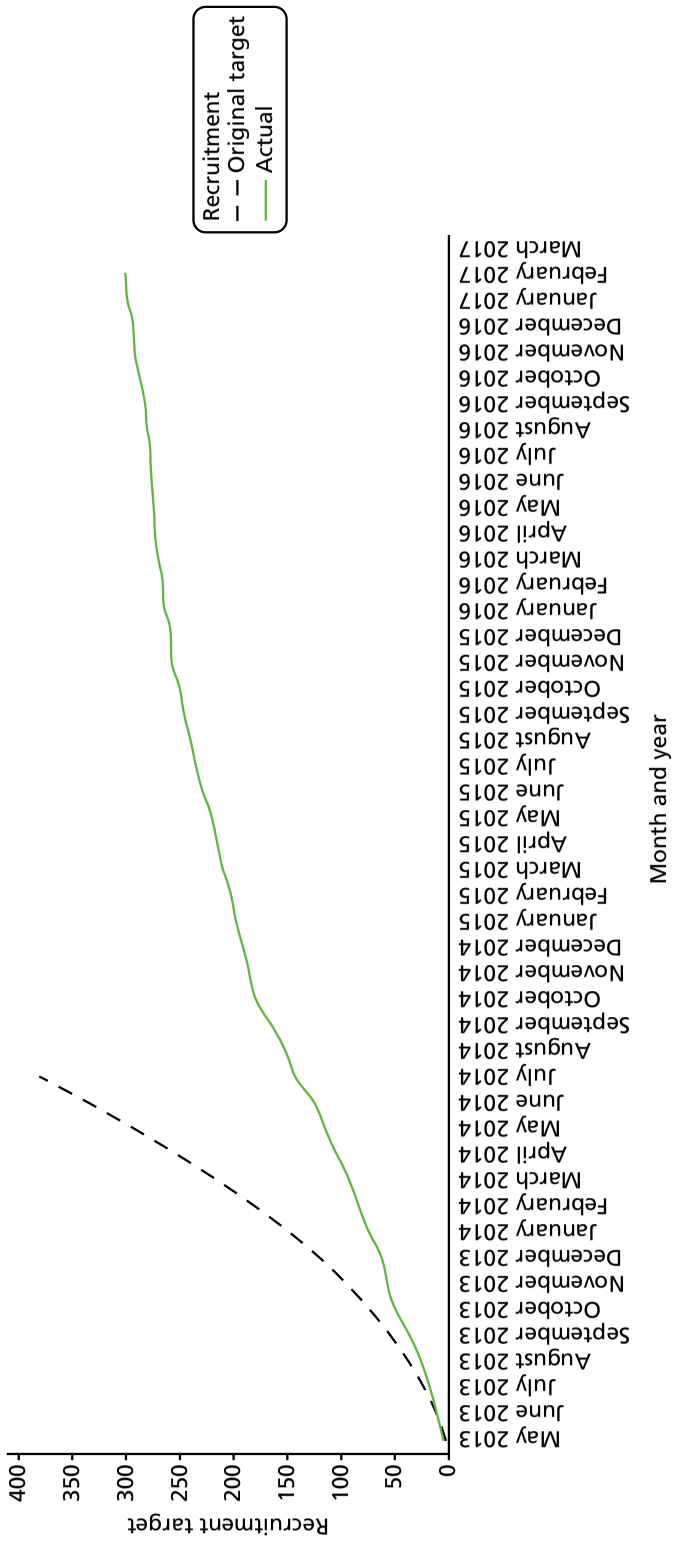


FIGURE 27 Cumulative recruitment.

TABLE 25 Recruitment by site

Site	Month started recruitment	Number randomised
Aberdeen	May 2013	10
Canterbury	May 2013	38
Dundee[a]	May 2013	0
Guy's and St Thomas'[a]	May 2013	1
Salford	May 2013	52
Sheffield	May 2013	11
Preston	September 2013	22
Portsmouth	August 2013	23
Mid Essex	August 2013	22
Manchester	December 2013	19
Leicester	December 2013	28
North Staffs	February 2014	4
Pennine	December 2013	6
Wolverhampton	February 2014	15
Highland	February 2014	5
Wirral	May 2014	1
Sussex	July 2014	8
Exeter	March 2015	3
Plymouth	July 2014	4
Southend	September 2014	8
Fife	March 2015	8
Gloucester	October 2015	3
Birmingham	July 2015	5
Imperial	July 2016	3
Colchester	November 2016	0
Basildon	November 2016	1
Total		300

a Closed early because of the poor recruitment rate (Dundee) and regulatory issues (Guy's and St Thomas').

Appendix 6 Health economic sensitivity analyses

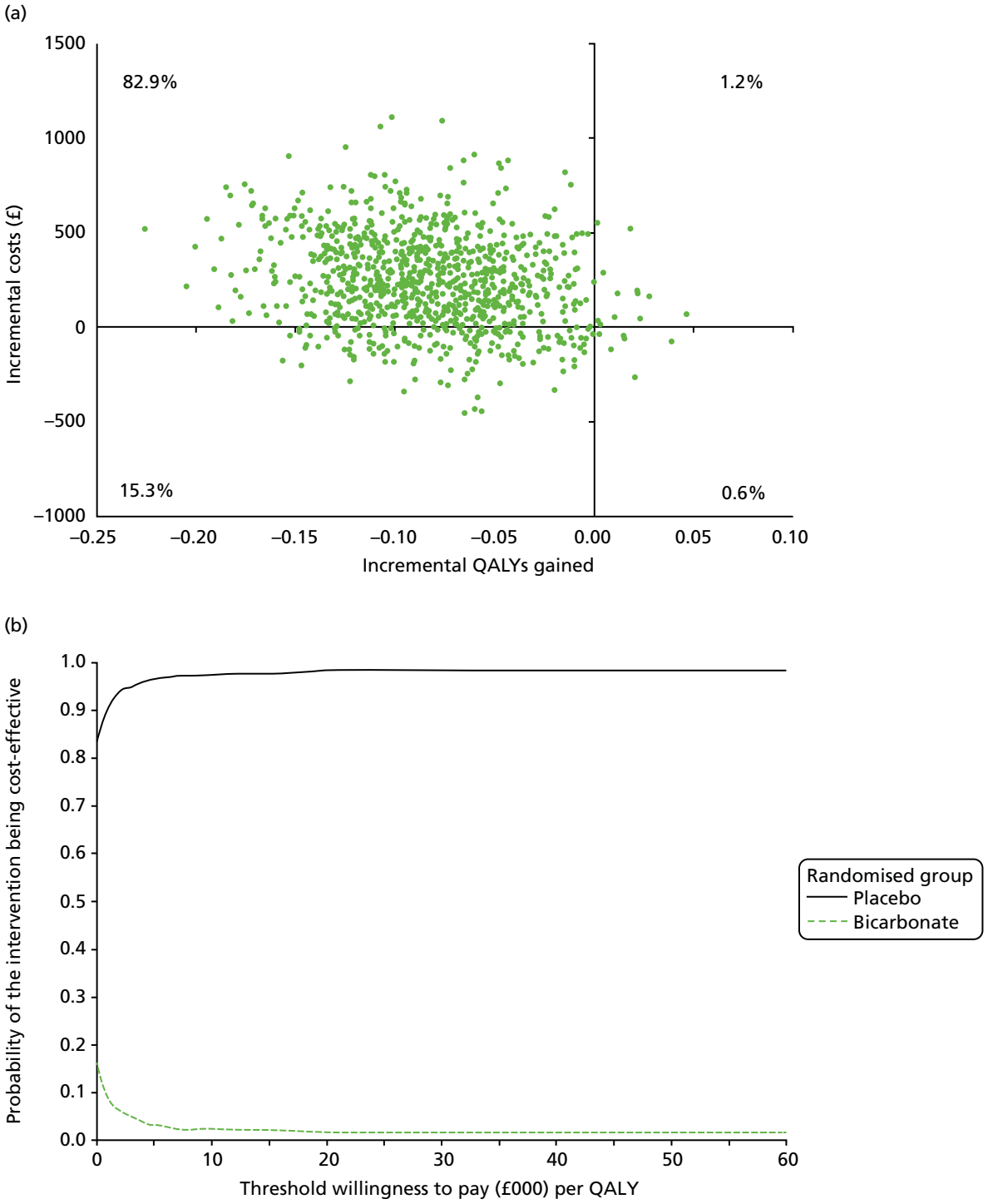
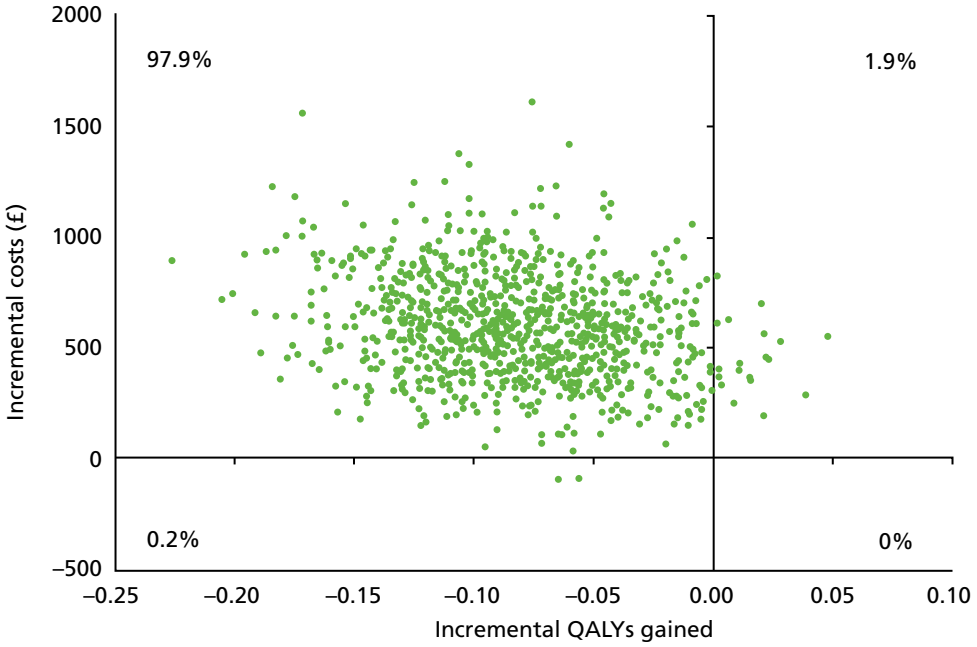


FIGURE 28 Sensitivity analyses of incremental cost difference and incremental ICECAP difference between randomised groups for complete cases over 24 months' follow-up ($n = 114$). (a) Scatterplot for lower sodium bicarbonate costs; (b) cost-effectiveness acceptability curve for lower sodium bicarbonate costs; (c) scatterplot for lower inpatient stay costs; (d) cost-effectiveness acceptability curve for lower inpatient stay costs; and (e) scatterplot for ICECAP values. (*continued*)

(c)



(d)

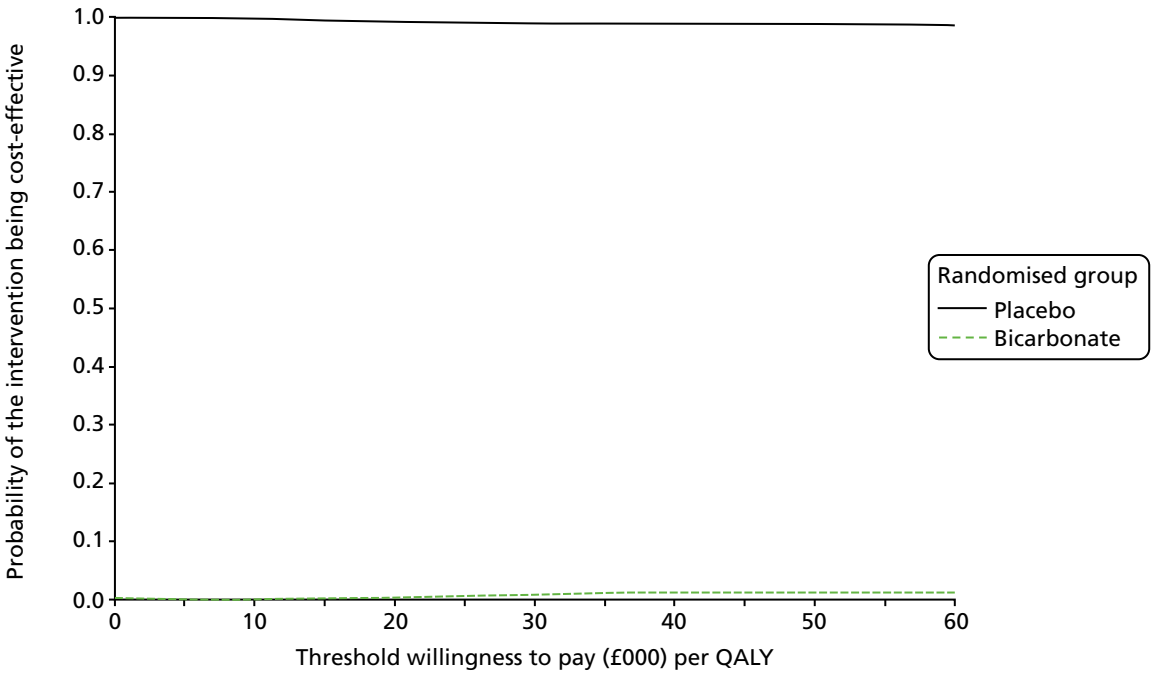


FIGURE 28 Sensitivity analyses of incremental cost difference and incremental ICECAP difference between randomised groups for complete cases over 24 months' follow-up ($n = 114$). (a) Scatterplot for lower sodium bicarbonate costs; (b) cost-effectiveness acceptability curve for lower sodium bicarbonate costs; (c) scatterplot for lower inpatient stay costs; (d) cost-effectiveness acceptability curve for lower inpatient stay costs; and (e) scatterplot for ICECAP values. (*continued*)

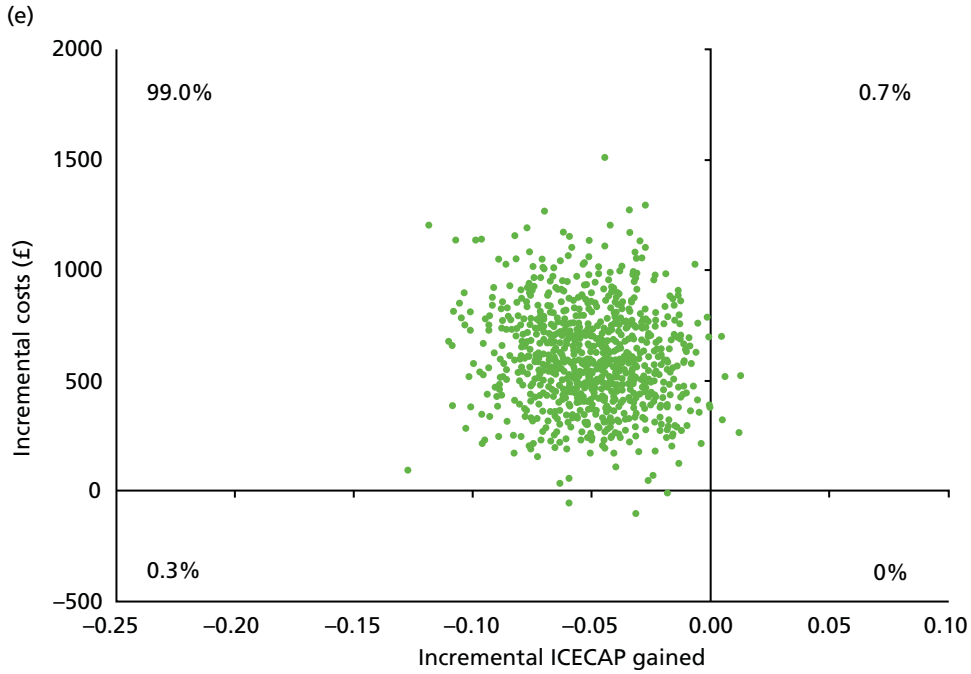


FIGURE 28 Sensitivity analyses of incremental cost difference and incremental ICECAP difference between randomised groups for complete cases over 24 months' follow-up ($n = 114$). (a) Scatterplot for lower sodium bicarbonate costs; (b) cost-effectiveness acceptability curve for lower sodium bicarbonate costs; (c) scatterplot for lower inpatient stay costs; (d) cost-effectiveness acceptability curve for lower inpatient stay costs; and (e) scatterplot for ICECAP values.

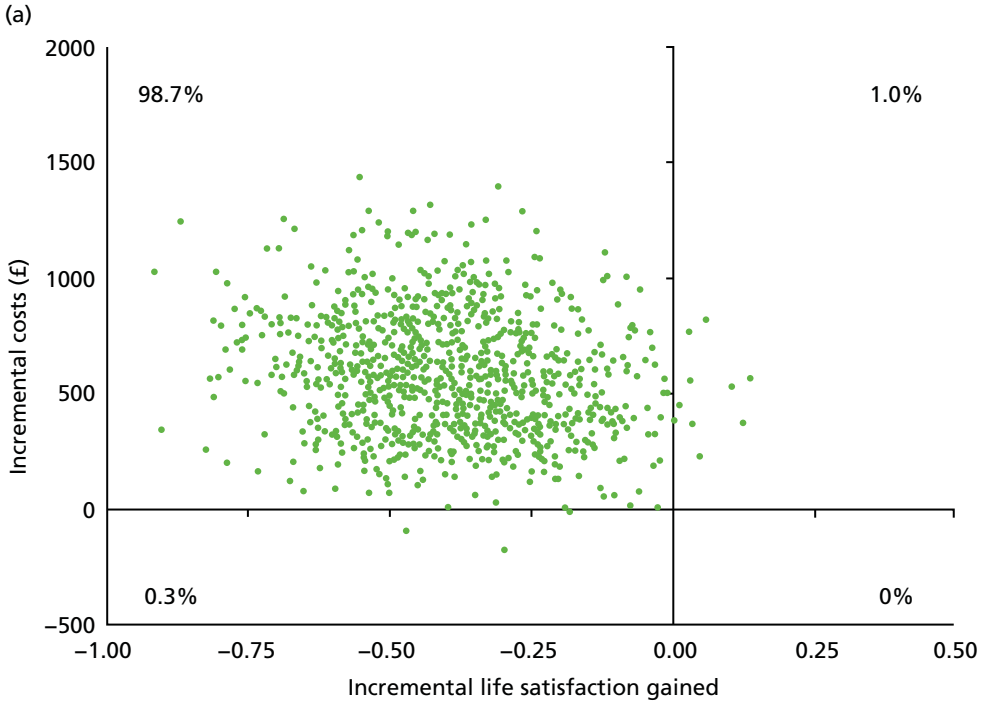


FIGURE 29 Sensitivity analyses of incremental cost difference and incremental life satisfaction difference between randomised groups. (a) Scatterplot for complete cases over 12 months' follow-up ($n = 176$); (b) scatterplot for complete cases over 24 months' follow-up ($n = 114$); and (c) scatterplot for complete cases over 24 months' follow-up and all particpants starting renal replacement therapy during the trial ($n = 159$). (*continued*)

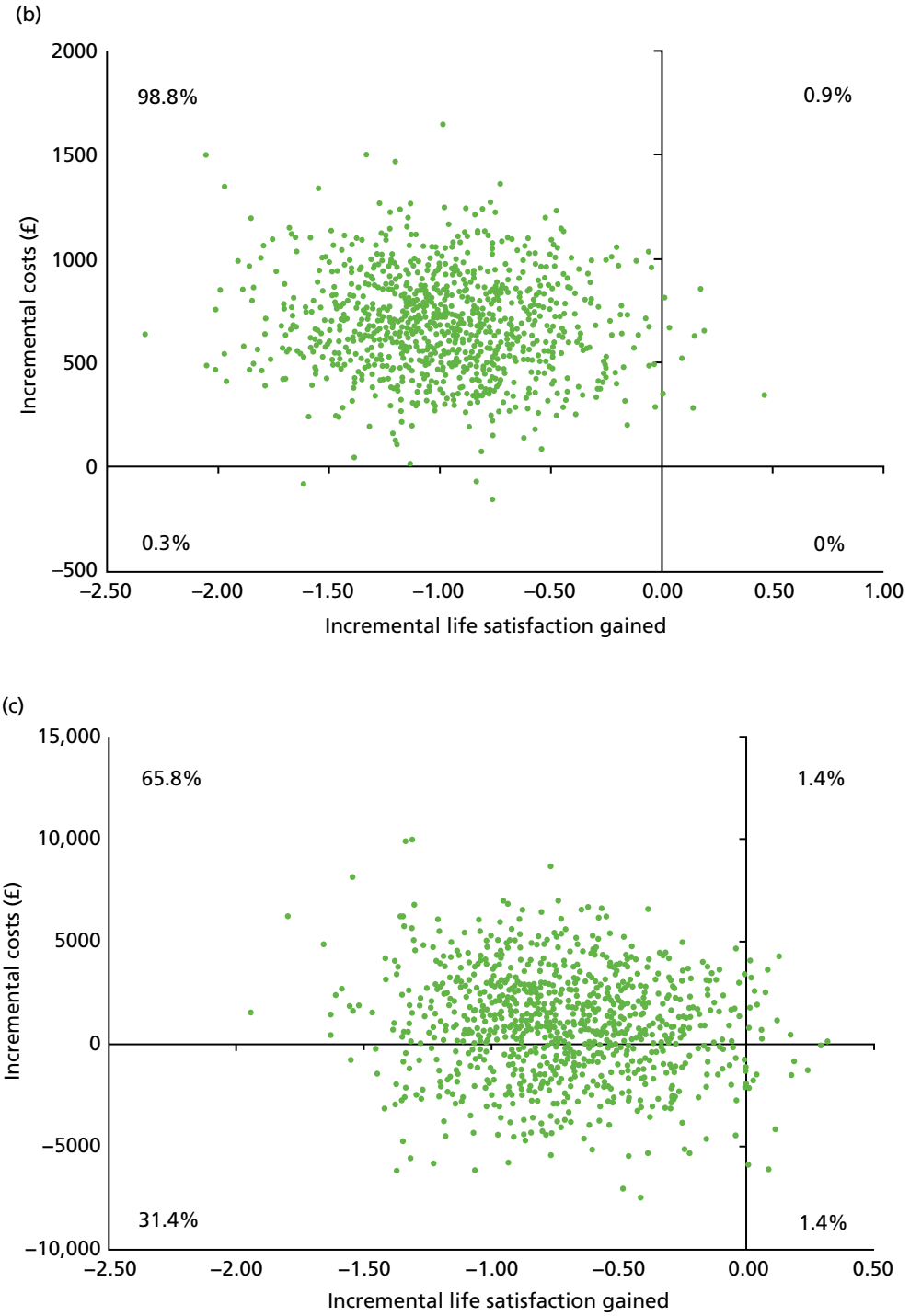


FIGURE 29 Sensitivity analyses of incremental cost difference and incremental life satisfaction difference between randomised groups. (a) Scatterplot for complete cases over 12 months' follow-up ($n = 176$); (b) scatterplot for complete cases over 24 months' follow-up ($n = 114$); and (c) scatterplot for complete cases over 24 months' follow-up and all particpants starting renal replacement therapy during the trial ($n = 159$).

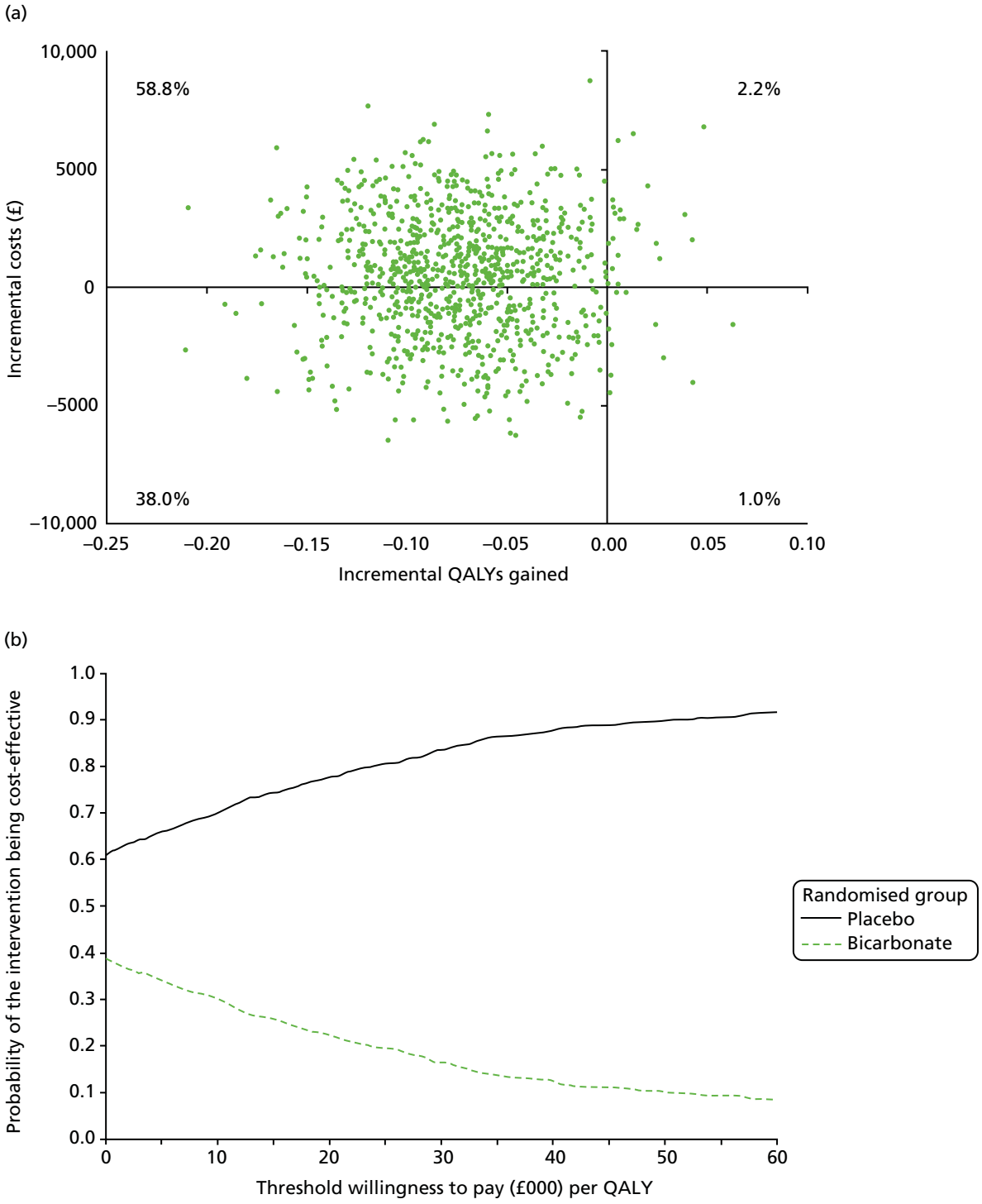


FIGURE 30 Sensitivity analyses of incremental cost difference and incremental QALY or ICECAP difference between randomised groups for complete cases over 24 months' follow-up and all participants starting renal replacement therapy during the trial. (a) Scatterplot for lower sodium bicarbonate costs; (b) cost-effectiveness acceptability curve for lower sodium bicarbonate costs; (c) scatterplot for lower inpatient stay costs; (d) cost-effectiveness acceptability curve for lower inpatient stay costs; (e) scatterplot for ICECAP values; (f) scatterplot for lower dialysis costs; (g) cost-effectiveness acceptability curve for lower dialysis costs; (h) scatterplot for higher dialysis costs; and (i) cost-effectiveness acceptability curve for higher dialysis costs. (*continued*)

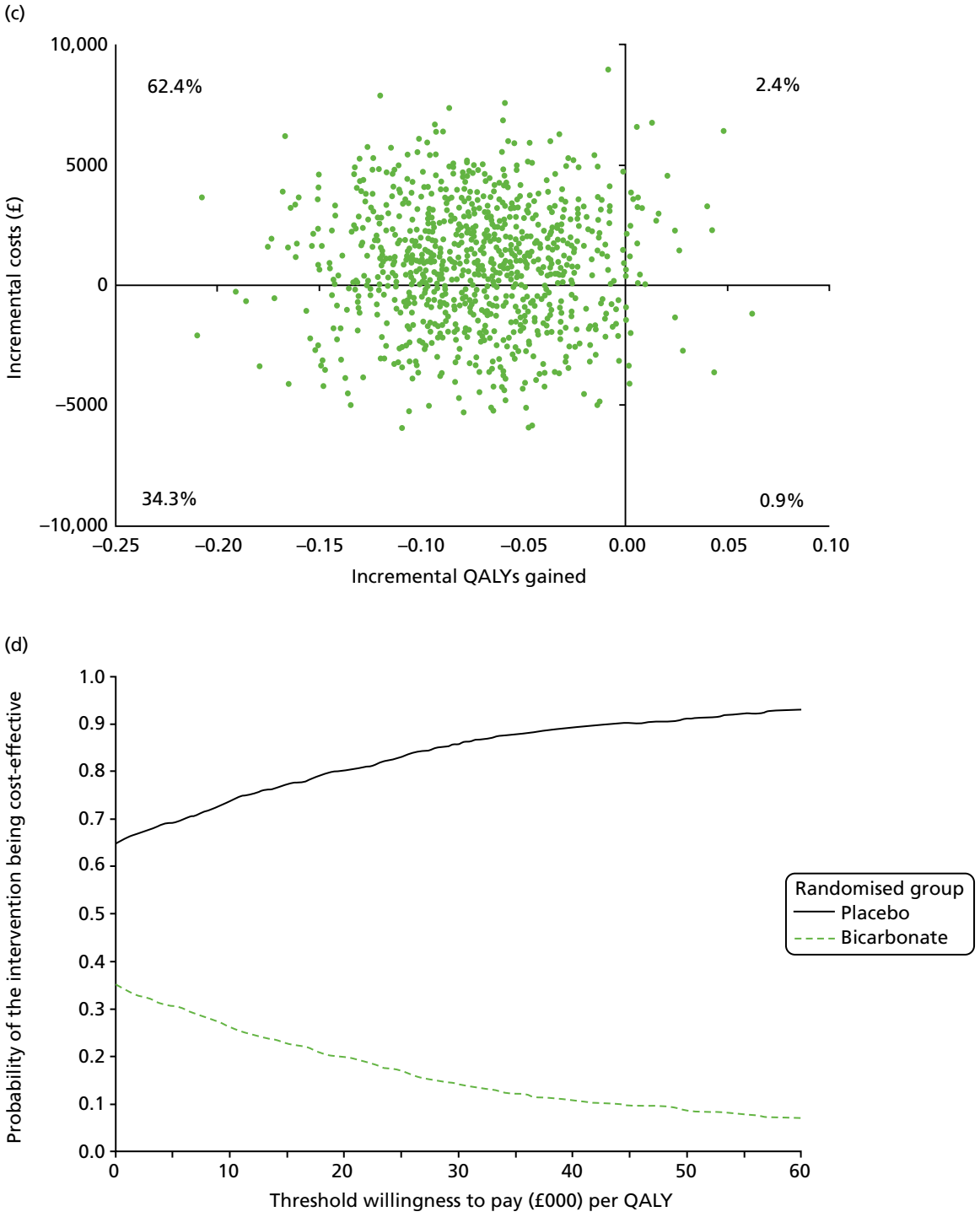


FIGURE 30 Sensitivity analyses of incremental cost difference and incremental QALY or ICECAP difference between randomised groups for complete cases over 24 months' follow-up and all participants starting renal replacement therapy during the trial. (a) Scatterplot for lower sodium bicarbonate costs; (b) cost-effectiveness acceptability curve for lower sodium bicarbonate costs; (c) scatterplot for lower inpatient stay costs; (d) cost-effectiveness acceptability curve for lower inpatient stay costs; (e) scatterplot for ICECAP values; (f) scatterplot for lower dialysis costs; (g) cost-effectiveness acceptability curve for lower dialysis costs; (h) scatterplot for higher dialysis costs; and (i) cost-effectiveness acceptability curve for higher dialysis costs. (*continued*)

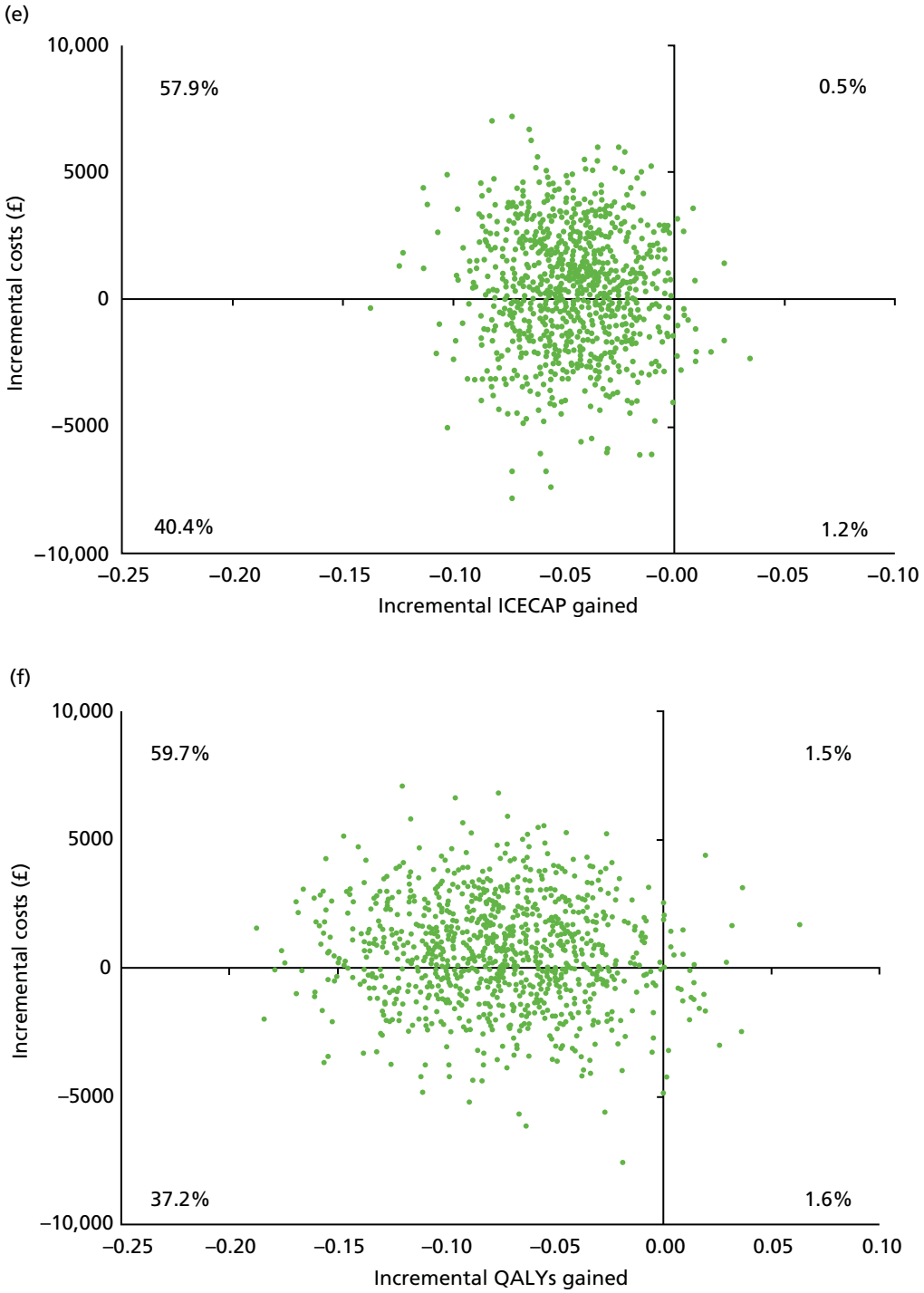
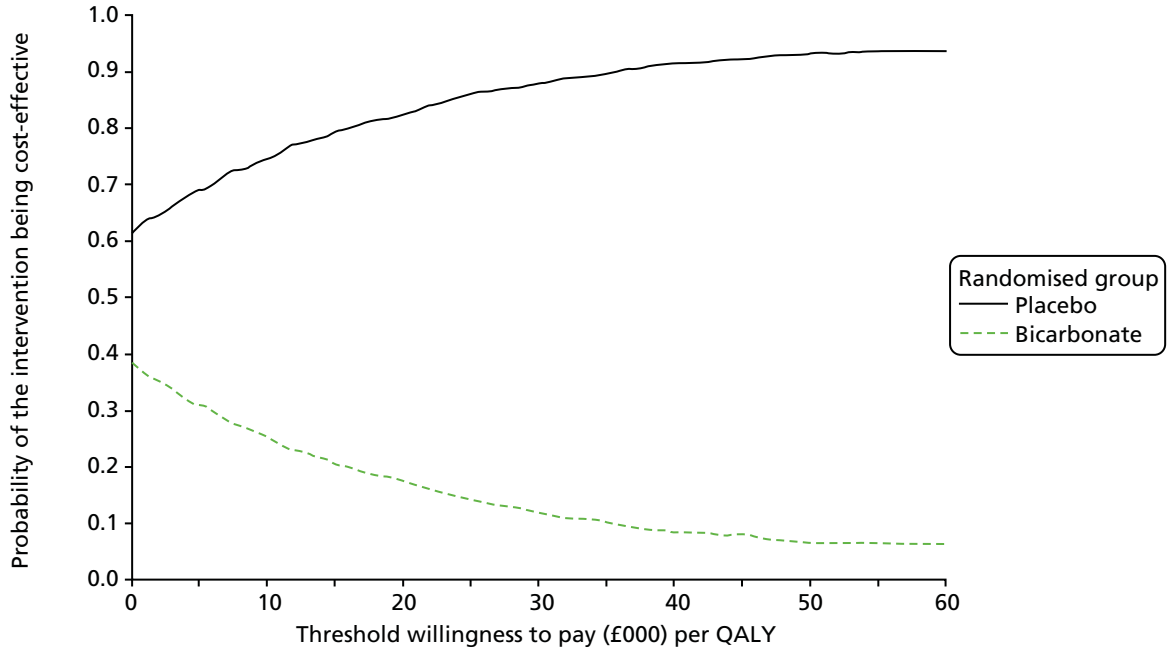


FIGURE 30 Sensitivity analyses of incremental cost difference and incremental QALY or ICECAP difference between randomised groups for complete cases over 24 months' follow-up and all participants starting renal replacement therapy during the trial. (a) Scatterplot for lower sodium bicarbonate costs; (b) cost-effectiveness acceptability curve for lower sodium bicarbonate costs; (c) scatterplot for lower inpatient stay costs; (d) cost-effectiveness acceptability curve for lower inpatient stay costs; (e) scatterplot for ICECAP values; (f) scatterplot for lower dialysis costs; (g) cost-effectiveness acceptability curve for lower dialysis costs; (h) scatterplot for higher dialysis costs; and (i) cost-effectiveness acceptability curve for higher dialysis costs. (*continued*)

(g)



(h)

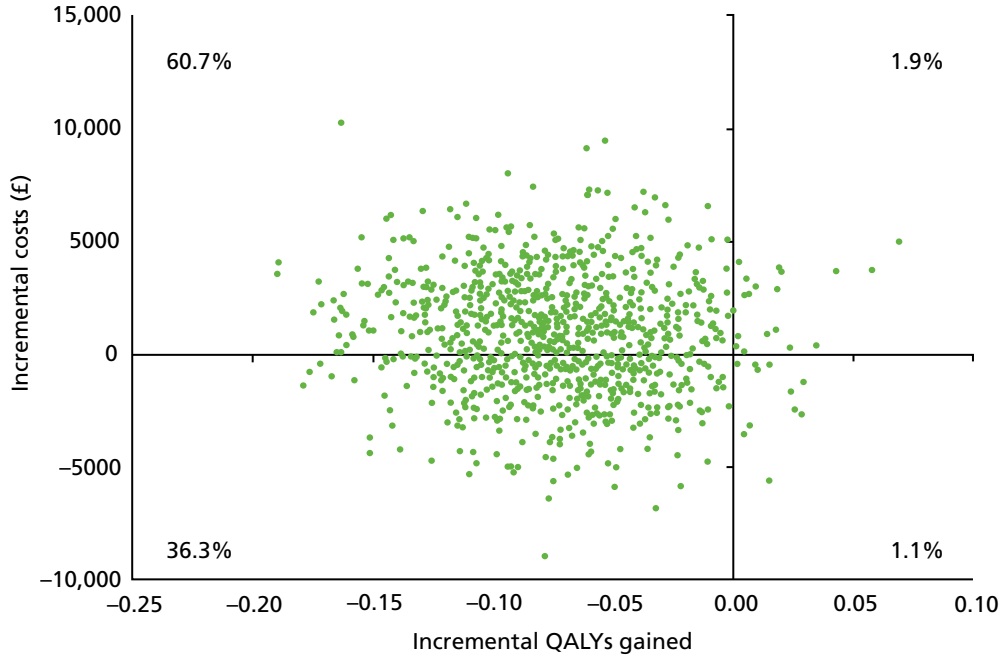


FIGURE 30 Sensitivity analyses of incremental cost difference and incremental QALY or ICECAP difference between randomised groups for complete cases over 24 months' follow-up and all participants starting renal replacement therapy during the trial. (a) Scatterplot for lower sodium bicarbonate costs; (b) cost-effectiveness acceptability curve for lower sodium bicarbonate costs; (c) scatterplot for lower inpatient stay costs; (d) cost-effectiveness acceptability curve for lower inpatient stay costs; (e) scatterplot for ICECAP values; (f) scatterplot for lower dialysis costs; (g) cost-effectiveness acceptability curve for lower dialysis costs; (h) scatterplot for higher dialysis costs; and (i) cost-effectiveness acceptability curve for higher dialysis costs. (*continued*)

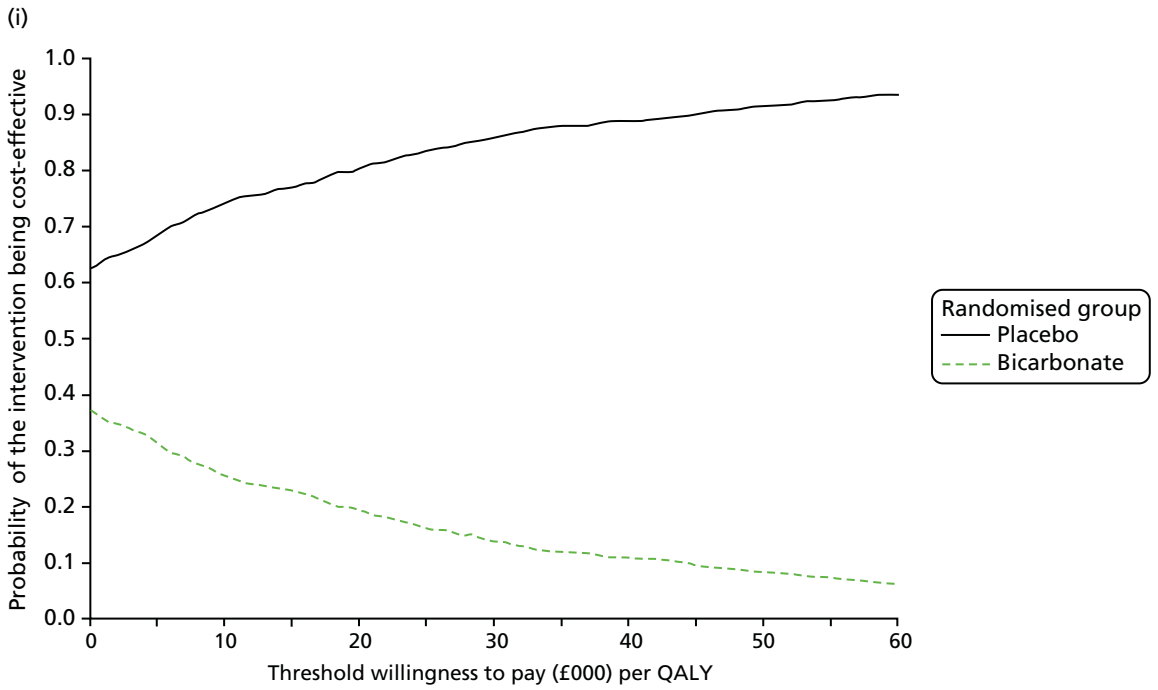


FIGURE 30 Sensitivity analyses of incremental cost difference and incremental QALY or ICECAP difference between randomised groups for complete cases over 24 months' follow-up and all participants starting renal replacement therapy during the trial. (a) Scatterplot for lower sodium bicarbonate costs; (b) cost-effectiveness acceptability curve for lower sodium bicarbonate costs; (c) scatterplot for lower inpatient stay costs; (d) cost-effectiveness acceptability curve for lower inpatient stay costs; (e) scatterplot for ICECAP values; (f) scatterplot for lower dialysis costs; (g) cost-effectiveness acceptability curve for lower dialysis costs; (h) scatterplot for higher dialysis costs; and (i) cost-effectiveness acceptability curve for higher dialysis costs.

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